NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Etelcalcetide for treating secondary hyperparathyroidism

Contents:

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

Premeeting briefing

Etelcalcetide for the treatment of secondary hyperparathyroidism [ID908]

This slide set is the premeeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Key issues for consideration

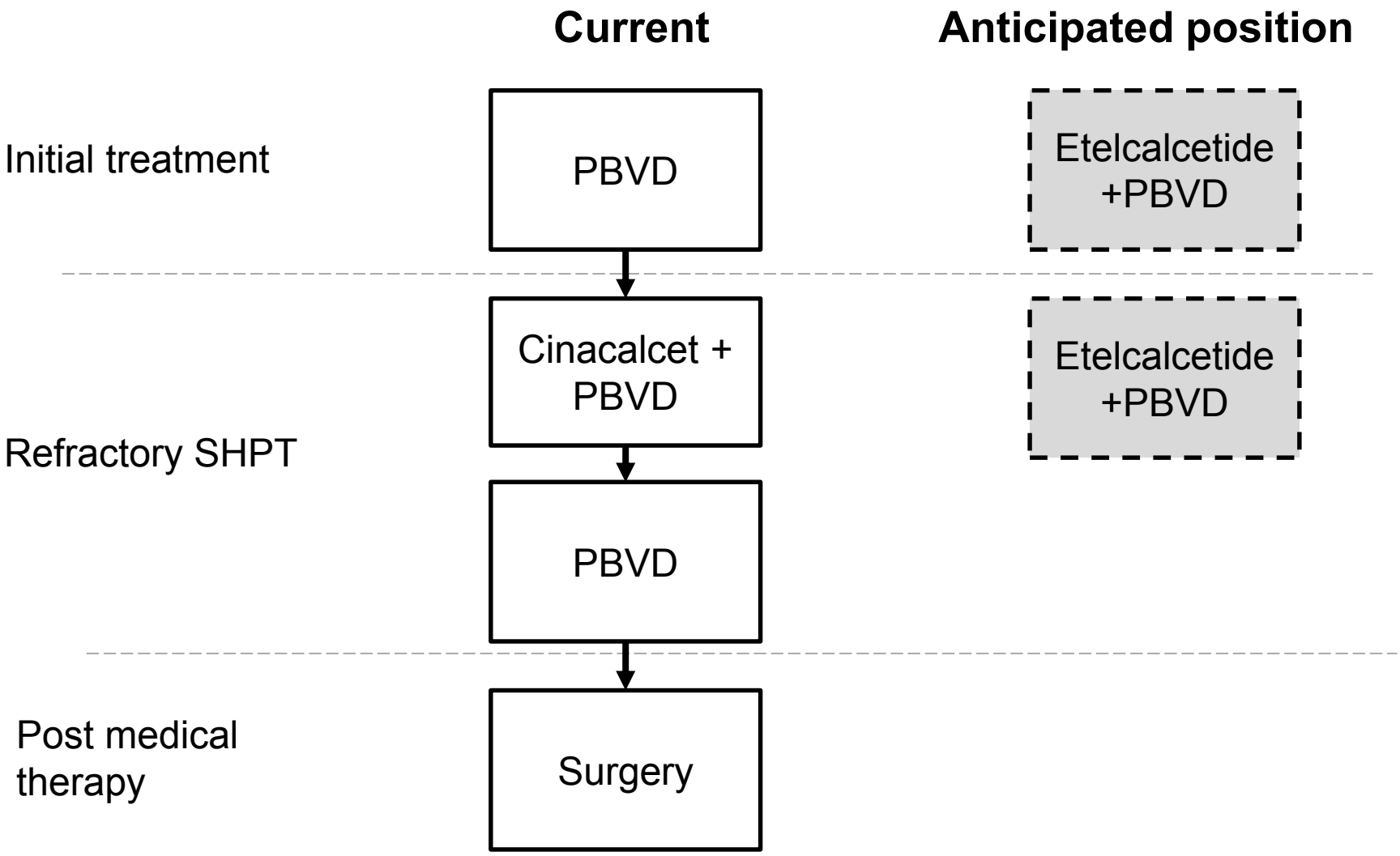
- How are patients treated in clinical practice, is NICE guidance on cinacalcet applied?
- Surrogate biochemical outcomes used in the clinical trials of etelcalcitide
  - Data from another trial (of cinacalcet) was used to predict the long term outcomes of survival & incidence of cardiovascular events. Is this reasonable?
- Is the primary outcome of 30% reduction in PTH level and/or a target of 300 pg/ml (or less) appropriate/generalisable to UK clinical practice?
- Was the approach to extrapolating treatment effects appropriate?
  - ERG agreed with log-linear method but company used a ‘naïve’ method of pooling data from the phase III etelcalcetide trials, which ERG considered inappropriate
- ERG highlighted that the relative efficacy of etelcalcetide and cinacalcet in patients wih refractory SHPT unclear
- Company model excluded longer-term savings or health effects that might be associated with parathyroidectomy. Is this appropriate?
- Innovation: IV vs oral therapy

Secondary hyperparathyroidism (SHPT)

- SHPT is a serious complication in patients with chronic kidney disease (CKD) on haemodialysis
- persistent elevations in levels of biochemical markers of mineral metabolism, including parathyroid hormone (PTH), calcium, and phosphate
- if inadequately controlled it is associated with vascular calcification and bone disease (increases risk of cardiovascular events, fractures and death) and reduced quality of life
- around 9,000 of the 21,000 patients on haemodialysis are estimated to be affected in England
- aim of treatment is to maintain parathyroid hormone, calcium and phosphorus levels within acceptable target ranges

Treatment pathway – company submission

(treatment initiated in people with uncontrolled PTH (>300 pg/ml))



Key: PBVD, phosphate binders + vitamin D

Decision problem

	Final scope issued by NICE
Population	People with SHPT with chronic kidney disease, receiving haemodialysis
Intervention	Etelcalcetide
Comparators	Established clinical practice without calcimimetic (dietary modification to restrict phosphate, phosphate binders, analogues of vitamin D) For people with refractory SHPT: Cinacalcet
Outcomes	The outcome measures to be considered include: • survival • incidence of fractures • incidence of cardiovascular events • need for parathyroidectomy • symptoms such as bone pain and itching or mobility • hospitalisation • serum levels of parathyroid hormone • serum levels of calcium and phosphate • health-related quality of life • adverse effects of treatment

Etelcalcetide - Description of the technology	
Marketing authorisation	Treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy
Pharmaceutical formulation	2.5 mg, 5 mg, 10 mg solution for injection (single-use glass vials).
Acquisition cost (excl. VAT) *	XXXXXXXXXXXXXXXXXXXX
Method of administration	Administered by bolus injection into the venous line of the dialysis circuit at the end of routine haemodialysis treatment during rinse back or intravenously after rinse back.
Doses	Starting dose is 5 mg 3 times per week during routine haemodialysis sessions. Doses should be titrated up or down so that doses are individualised between 2.5 mg and 15 mg 3 times per week. Treatment is anticipated to be ongoing

Patient perspective *(British Kidney Association; Kidney Research UK)*

- Secondary hyperparathyroidism affects both mental and physical health.
- Symptoms include bone pain, stomach pain, fatigue, confusion, nausea & depression leading to mobility problems, sleeplessness and reduced QoL.
- Current NHS treatments do not work for some patients.
- Drug regimes are burdensome. Surgery carries extra risk and isn't always successful.
- Patients want relief from symptoms, better control of their condition and for different treatment options to be made available.

Patient perspective

Patients and carers have indicated that they expect etelcalcetide to have the following advantages:

- Reduction of pain; Increased mobility; Less need for surgery.
- Patients dialysing in hospital do not have the worry of taking another oral medication, as for the first time a calcimimetic will be administered through IV, thus reducing the pill burden.
- However, people who are on home dialysis and those with transplants are less likely to want to attend hospital 3 times a week to receive this treatment.

Equality Issues

Raised by the British Kidney Association:

- *"There are kidney patients who are or may be given current treatments off-label, as they are not on dialysis. They may be post-transplant or pre-dialysis and still have secondary PTH and be symptomatic. We would not wish new guidance to impact on this flexibility. There may also be patients with PTH under 800 who benefit from treatment. New treatments should continue for these patients as well."*

Clinical effectiveness evidence

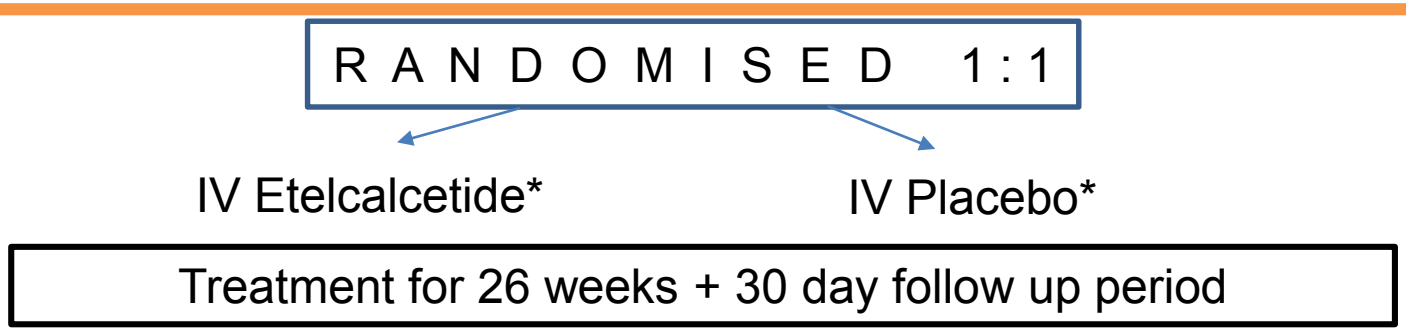
Clinical trial evidence: etelcalcetide vs placebo

Two phase 3, randomised, double-blind, placebo-controlled trials

NCT20120229 (n=508) **NCT20120230 (n=515)**

Population

- Adults with CKD receiving haemodialysis 3 times per week for ≥ 3 months
- Stable calcium ≥ 8.3 mg/dL (2.075 mmol/L) and PTH > 400 pg/mL (42.4 pmol/L)



Primary outcome:

- proportion of people with >30% reduction from baseline in PTH levels (assessed during Efficacy Assessment Phase wks 20-27)

Secondary outcomes:

- Proportion of people with predialysis PTH ≤ 300 pg/mL in wks 20-27
- % change from baseline in predialysis PTH, cCa, cCa x P and P in wks 20-27.

*Both groups could receive active vitamin D, phosphate binders, and calcium supplements

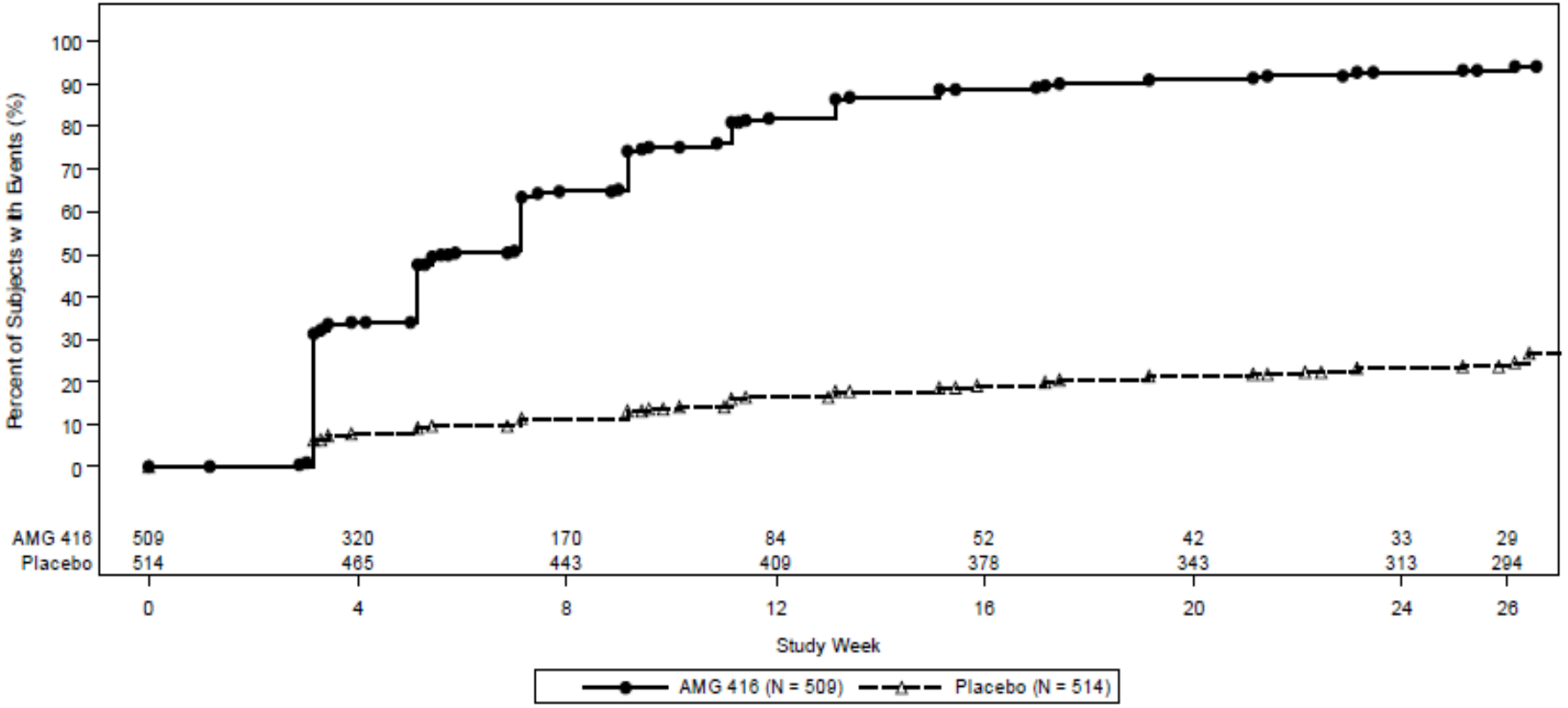
Pooled results for studies 20120229 and 20120230

	Pooled	
	Placebo (N = 514)	Etelcalcetide (N = 509)
Primary outcome		
Achievement of a > 30% reduction in mean PTH from baseline during EAP, n (%)	46 (**8.9%**)	380 (**74.7%**)
Odds ratio[a] (95% CI)	31.60 (21.59, 46.25)	
P value	<0.001	
Secondary outcome		
Achievement of mean PTH ≤ 300 pg/mL during EAP, n (%)	25 (**4.9%**)	262 (**51.5%**)
Odds ratio[a] (95% CI)	27.02 (16.62, 43.93)	
P value	<0.001	

CI, confidence interval; EAP, Efficacy Assessment Phase (weeks 20-27); n, number of patients with observed data; P, phosphate; PTH, parathyroid hormone; SE, standard error

[a] Cochran-Mantel-Haenszel (CMH) stratified odds ratio (etelcalcetide:placebo). P value from CMH test.

Kaplan-Meier estimates of time to first occurrence of PTH > 30% reduction from baseline (6-month placebo-controlled pooled dataset – Full Analysis Set)



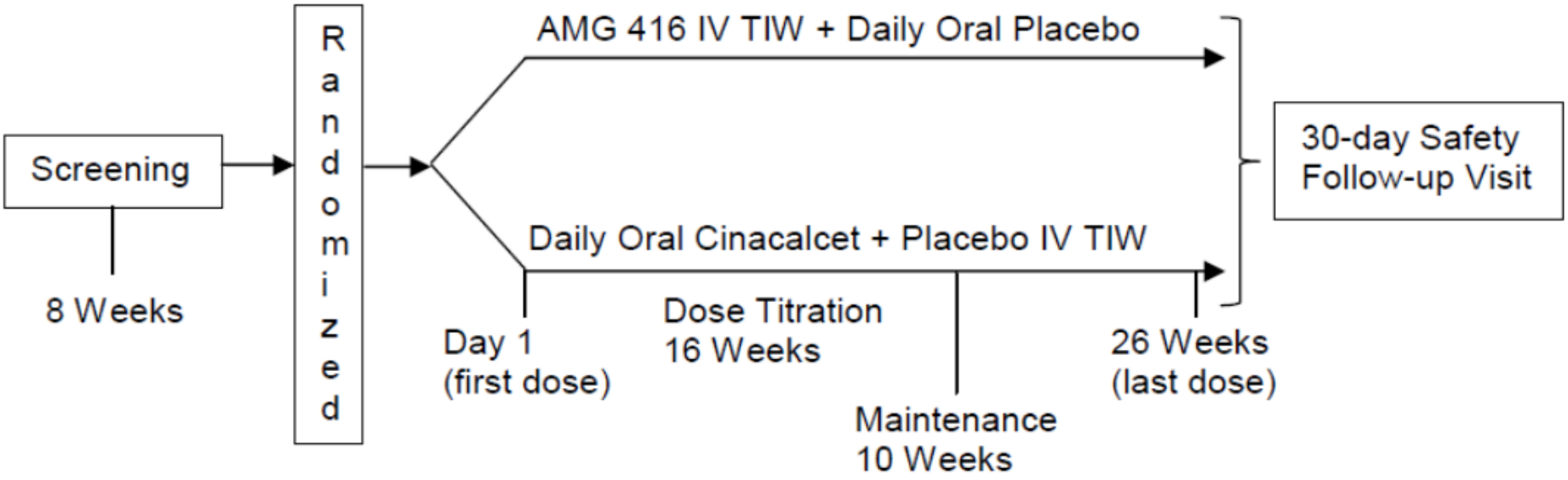
Rolling averages of 3 iPTH values instead of single time point values were used.

Etelcalcetide vs cinacalcet NCT20120360

(Note: not confined to those with refractory disease as per NICE guidance)

Population

- Adults with CKD receiving haemodialysis 3 times per week for ≥ 3 months
- Stable calcium (≥ 8.3 mg/dL) and **PTH levels of > 500 pg/mL (53 pmol/L)**



Primary outcome:

Non-inferiority vs cincalcet for lowering PTH levels by >30% from baseline (assessed during EAP at wks 20-27)

Secondary outcome (sequential test for superiority):

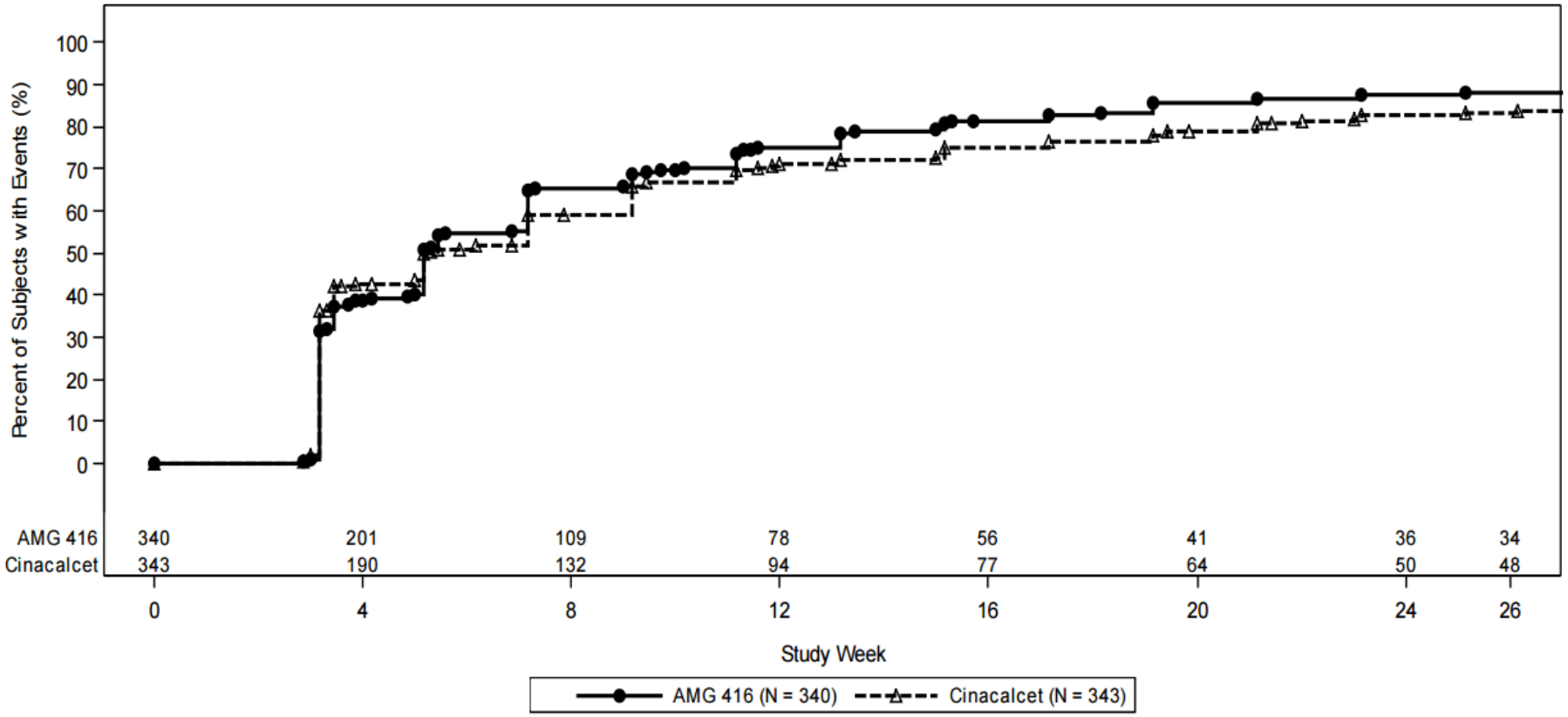
- Proportion of people with >50% reduction in PTH,
- Proportion of people with >30% reduction in PTH

Summary of results for the primary and secondary efficacy endpoints in the active-controlled phase 3 study (NCT20120360)

	Cinacalcet (N=343)	Etelcalcetide (N=340)
Primary Endpoint (Non-inferiority)		
> 30% reduction in mean PTH from baseline (%)	**63.9%**	**77.9%**
	Stratified treatment difference -10.48% (95% CI, -17.45, -3.51)	
Key Secondary Endpoints (Superiority)		
> 50% reduction in mean PTH from baseline during EAP, n (%)	**40.2%**	**52.4%**
	Odds ratio 1.65 (95% CI, 1.21, 2.23), p-value = 0.001	
> 30% reduction in mean PTH from baseline during EAP, n (%)	**57.7%**	**68.2%**
	Odds ratio 1.59 (95% CI, 1.16, 2.17) p-value = 0.004	
Mean number of days of vomiting or nausea per week in the first 8 weeks (Adjusted mean)	**0.3 (0.03)** (n=324)	**0.4 (0.04)** (n=331)
	Estimated treatment difference **1.2** (SE, 0.15; 95% CI 0.89, 1.49; p-value = 0.27)	

CI, confidence interval; EAP, Efficacy Assessment Phase (weeks 20-27); n, number of patients with observed data; P, phosphate; PTH, parathyroid hormone; SE, standard error

Kaplan-Meier estimates of time to first occurrence of PTH > 30% reduction from baseline (Study 20120360)



Key:
AMG 416, etelcalcetide; PTH, parathyroid hormone

Clinical efficacy - subgroups

Pre-specified subgroup analyses

- Studies 20120229, 20120230 and 20120360
  - Based on demographics, severity of SHPT and prior use of cinacalcet
  - Company state that superior efficacy of etelcalcetide over the comparators was consistent across all pre-defined patient subgroups

ERG comments

- Agree that there were no significant differences in efficacy between the whole trial populations and the pre-specified subgroups
- Caution required as the subgroup analyses were not statistically powered to detect treatment differences

Long term efficacy open-label extension study 20120231 (OLE1)

OLE1 20120231 (n=891) Multicentre single-arm, 52-week extension study to parent studies 20120229, 20120230, and 20120359		
Results		
	>30% reduction from baseline PTH (%, 95%CI)	**PTH ≤300pg/mL (%, 95%CI)**
EAP6	68.1% (64.6% to 71.4%)	55.5% (52.0% to 59.1%)
EAP12	67.5% (63.8%, to71.0%)	56.4% (52.6% to 60.0%)
EAP	67.7% (64.2% to 70.9%)	57.3% (53.8% to 60.7%)
EAP= efficacy assessment phase; IV = intravenous;		

- Company stated that OLE1 showed continued reductions in PTH, calcium and phosphorus are observed, with long-term treatment

Note: 300 pg/mL is equivalent to 31.8 pmol/L

Health-related quality of life

- Collected as part of study **20120360** (etelcalcetide vs cinacalcet)
- Measured using KDQOL-36 (has 5 sub-scales ….
- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXX
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXX
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXX
- The company did not use these results in the economic base case analysis and no HRQoL benefit is assumed for calcimimetic treatment in the base case (although a scenario analyses explored this)
- ERG agrees XXXXXXXXXXXXXXXXXXin HRQoL scores from the KDQOL-36 results, the company's approach was reasonable

Overview of incidence of adverse events in etelcalcetide RCTs

	Total placebo-controlled studies		Study 20120360	
	Placebo (n=513)	Etelcalcetide (n=503)	Cinacalcet (n=341)	Etelcalcetide (n=338)
All treatment emergent AEs –n (%)	410 (79.9)	461 (91.7)	307 (90.0)	314 (92.9)
SAEs –n (%)	149 (29.0)	130 (25.8)	93 (27.3)	85 (25.1)
AEs leading to drug withdrawal –n (%)	13 (2.5)	9 (1.8)	16 (4.7)	19 (5.6)
Fatal AEs –n (%)	15 (2.9)	11 (2.2)	6 (1.8)	9 (2.7)

AEs=adverse events; SAE=serious adverse events
Source: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Incidence of AEs occurring in ≥ 5% of people in the etelcalcetide group (with ≥ 1% difference from placebo or cinacalcet) in phase 3 RCTs

	Total placebo-controlled studies		Study 20120360	
Preferred term	Placebo, % (N = 513)	Etelcalcetide % (N = 503)	Cinacalcet, % (N = 341)	Etelcalcetide % (N = 338)
Blood calcium decreased (asymptomatic)[a]	10.1	63.8	**59.8**	**68.9**
Muscle spasms	6.6	11.5	**5.9**	**6.5**
Diarrhoea	8.6	10.7	10.3	6.2
Nausea	6.2	10.7	22.6	18.3
Vomiting	5.1	8.9	13.8	13.3
Headache	6.0	7.6	7.0	6.5
Hypocalcaemia (symptomatic)[b]	0.2	7.0	2.3	5.0
Hypotension	5.1	6.0	**2.9**	**6.8**

AE, adverse event

[a] asymptomatic reduction in serum corrected calcium below 7.5 mg/dL (1.875 mmol/L) or asymptomatic reduction in serum corrected calcium between 7.5 and < 8.3 mg/dL (1.875 to <2.075 mmol/L) requiring medical management or deemed clinically significant by the investigator

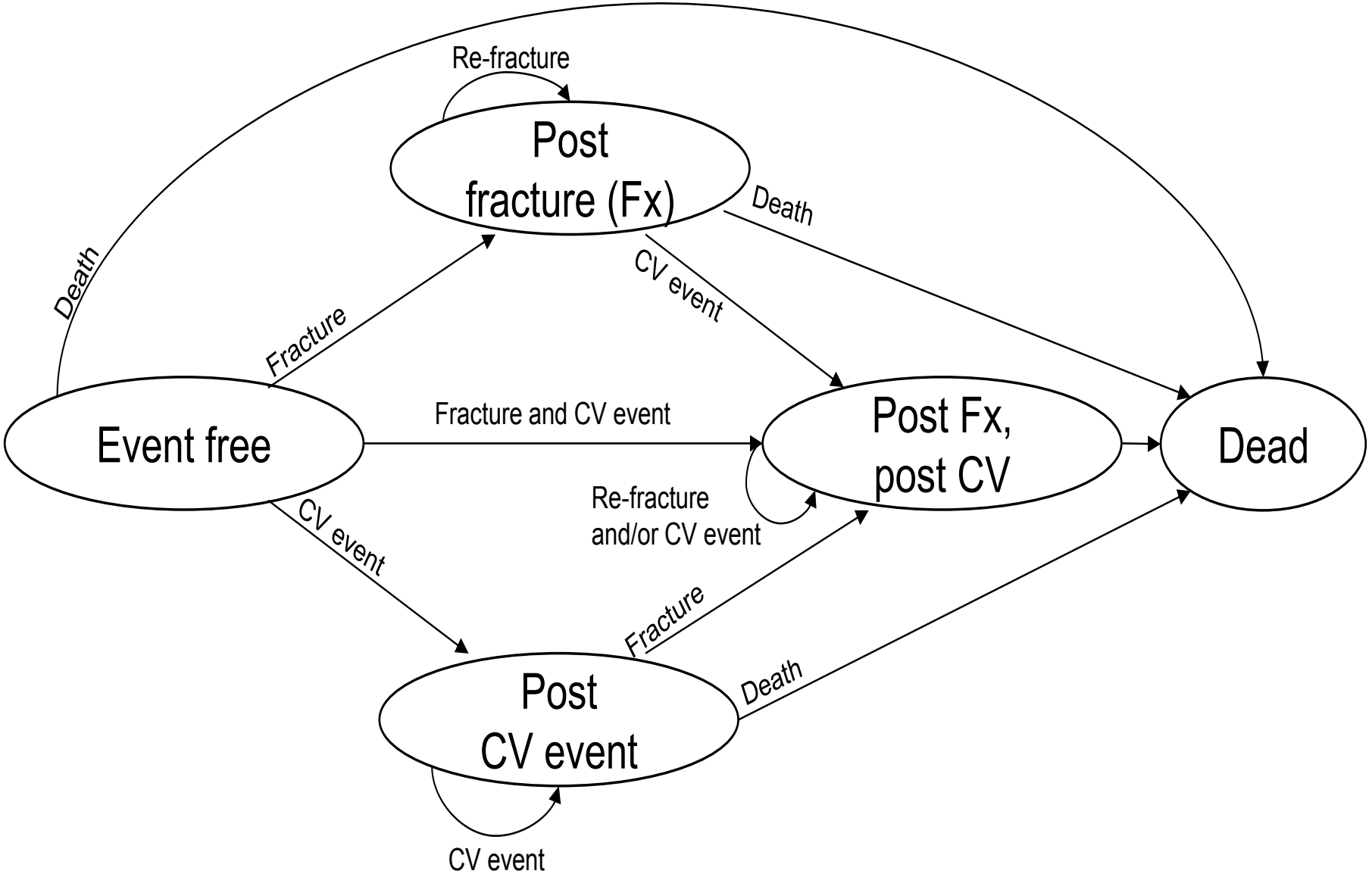
[b] symptomatic reduction in serum corrected calcium < 8.3 mg/dL (2.075 mmol/L)

ERG comments clinical effectiveness

- Good quality trials although
  - unclear if double-blinding was preserved, some results not ITT (risk of attrition bias)
- People included in trials were generally representative of those seen in practice in the UK
- Submission may not provide evidence about the efficacy of etelcalcetide vs cinacalcet in refractory SHPT population
  - Trial included broad population of patients with SHPT, rather than those with refractory SHPT
- Trials did not measure the longer-term clinically relevant outcomes specified in the scope
- Drug doses in the 3 trials were titrated to a PTH target of <300pg/mL (31.8 pmol/L)
  - ERG suggest that in practice 130 – 600 pg/mL (13.8 – 63.6 pmol/L) would be acceptable depending on Ca and P parameters
- Target used in trials did not include a lower range cut-off, therefore some at risk of PTH oversuppression (could impact longer term outcomes and cost effectiveness)

Cost effectiveness evidence

Cost effectiveness model



The basic model structure is repeated for the three modelled treatment options: etelcalcetide, cinacalcet and PB/VD (see also figure 3 of the ERG report).

Treatment effects

- Primary outcome of the etelcalcetide clinical trials was proportion of patients that achieved >30% PTH reduction over 6 months
- However, the model requires long term effects on clinical outcomes including mortality, CV events, fractures and PTx.
- The company base case extrapolated from primary outcome in etelcalcetide trials to HRs for clinical outcomes from EVOLVE trial
- EVOLVE was a placebo-controlled RCT of cinacalcet that measured effects on mortality, CV events, fractures & PTx with 5 year follow up
- However, EVOLVE had baseline imbalance in age and high discontinuation and treatment cross-over. Company presented 5 methods to adjust for these confounding factors.
- The company also presented a scenario analysis using a published risk prediction equation (Eandi et al) to estimate HRs from biomarker data from etelcalcetide trials

Methods to estimate treatment effects

The company submission presented six methods for estimating treatment effects in their economic model

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

EVOLVE trial: cinacalcet vs placebo

Population
- Adults with CKD receiving haemodialysis 3 times per week for ≥ 3 months
- PTH ≥ 300 pg/mL (31.8 pmol/L): median ~ 700 pg/mL (74.2 pmol/L)
- Calcium ≥ 8.4 mg/dL (2.1 mmol/L)

Cinacalcet + PB/VD (n=1948)
1300 discontinued study drug
(median exposure, 21.2 months)
222 started commercial cinacalcet

Placebo + PB/VD (n=1935)
1365 discontinued study drug
(median exposure 17.5 months)
440 started commercial cinacalcet

Primary outcome:
- Composite endpoint: time to death or first nonfatal CV event (MI, UA, HF, PVE)

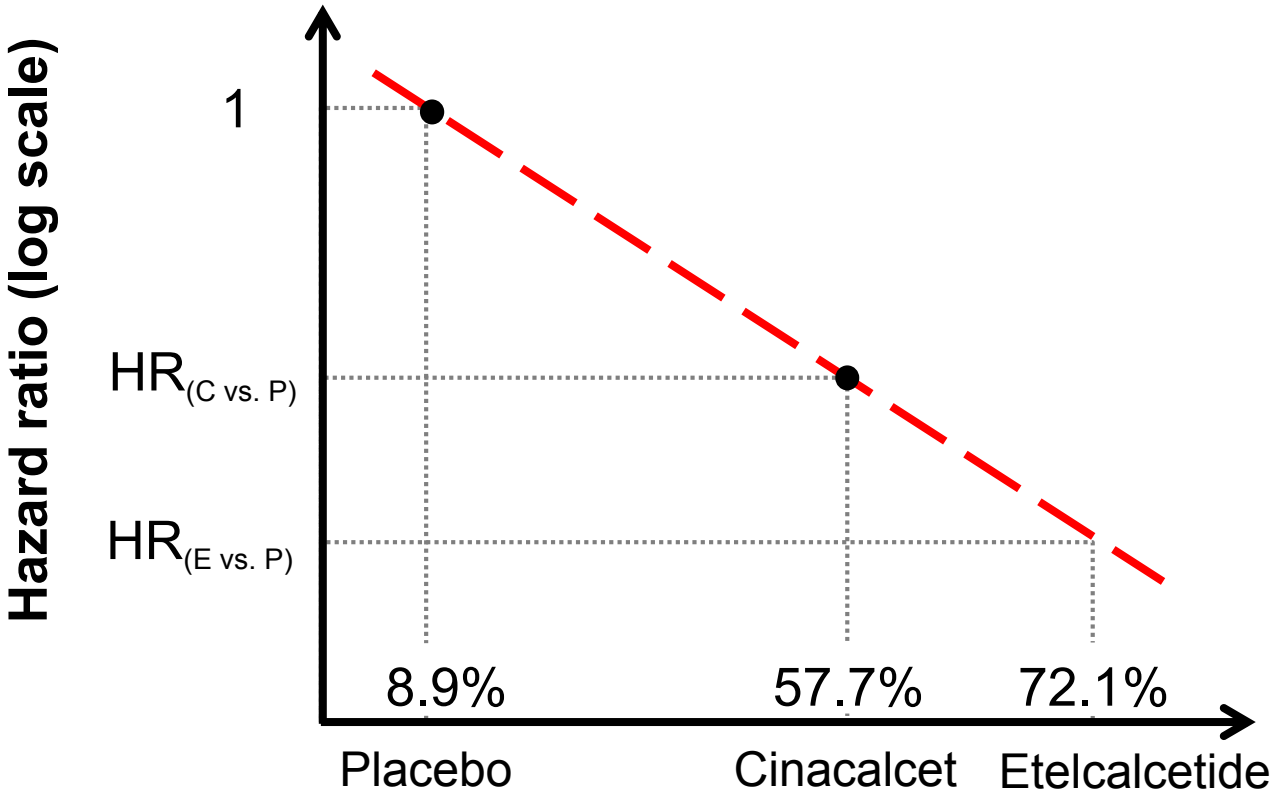
Secondary outcomes:
- Time to individual components of composite endpoint
- Time to stroke, bone fracture & PTx
- Biochemical measurements (% achieving >30% reduction in PTH not reported)

EVOLVE trial: results

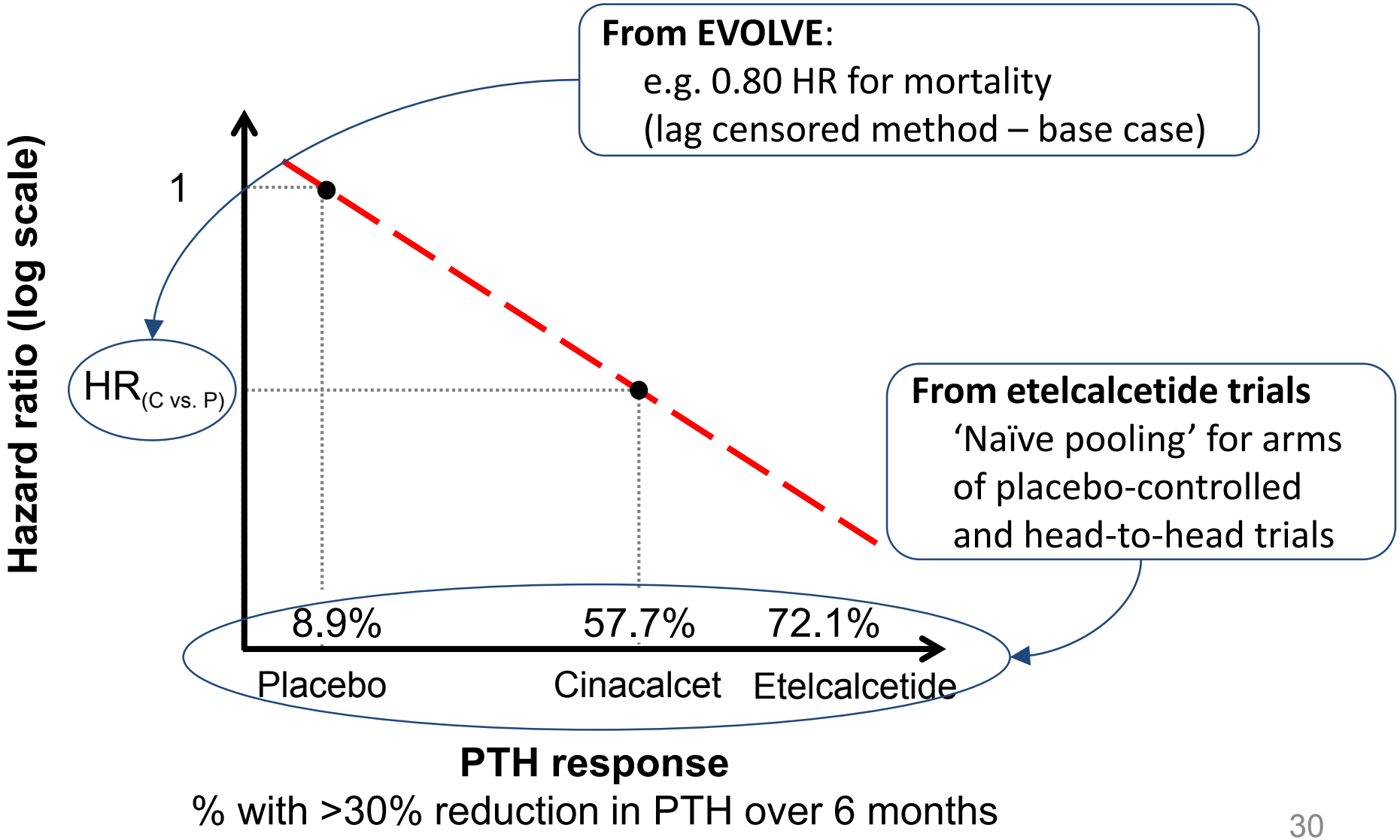
Method of analysis	All-cause mortality	Nonfatal CV event	Bone fracture	PTx
ITT	XXXXX XXXXX]	XXXXX XXXXX]	XXXXX XXXXX]	XXXXX XXXXX]
ITT adjusted *	0.87 [0.78, 0.97]	0.85 [0.74, 0.97]	0.86 [0.72, 1.04]	0.42 [0.34, 0.51]
Lag-censored (base case) *	**0.80 [0.69, 0.91]**	**0.78 [0.67, 0.91]**	**0.73 [0.59, 0.92]**	**0.25 [0.19, 0.33]**
Disaggregated ITT *	0.78 [0.63, 0.95]	0.76 [0.59, 0.95]	0.77 [0.55, 1.06]	0.06 [0.00, 0.20]
RPSFTM *	XXXXX XXXXX]	XXXXX XXXXX]	XXXXX XXXXX]	XXXXX XXXXX]
IPE *	XXXXX XXXXX]	XXXXX XXXXX]	XXXXX XXXXX]	XXXXX XXXXX]

* Adjusted for baseline covariates

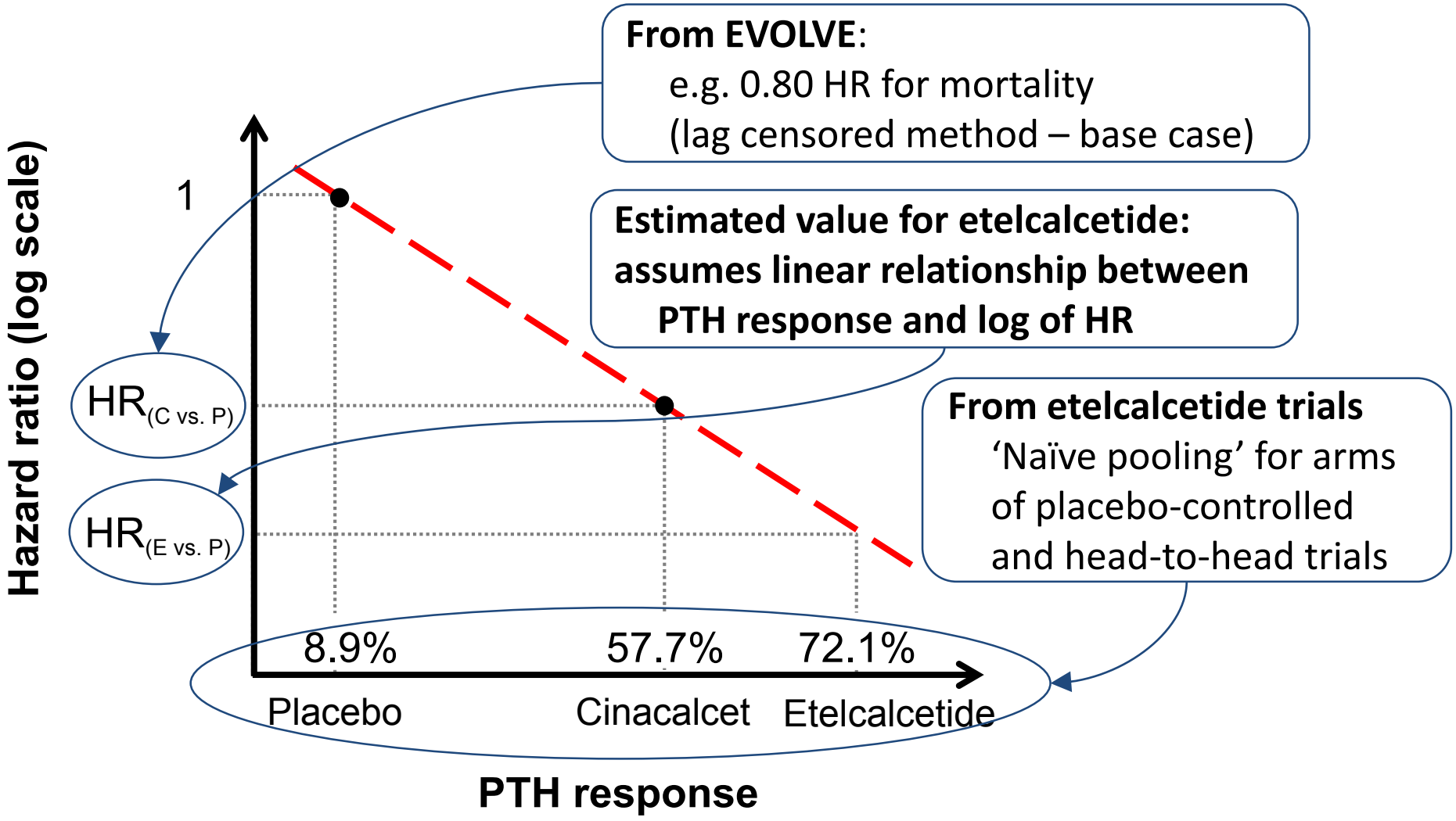
Extrapolation of EVOLVE HRs to etelcalcetide



Extrapolation of EVOLVE HRs to etelcalcetide



Extrapolation of EVOLVE HRs to etelcalcetide



Estimate of HRs of etelcalcetide based on extrapolation from EVOLVE trial

	Lag-censored HR's[1] [95% CI]	Source
Etelcalcetide vs. cinacalcet		Stollenwerk 2016
All-cause mortality	**0.94 [0.88, 0.98]**	
CV events (non-fatal)	**0.93 [0.87, 0.98]**	
Fractures (non-fatal)	**0.91 [0.83, 0.98]**	
PTx (non-fatal)	**0.66 [0.51, 0.81]**	
Etelcalcetide vs. placebo		
All-cause mortality	**0.75 [0.62, 0.89]**	
CV events (non-fatal)	**0.72 [0.59, 0.88]**	
Fractures (non-fatal)	**0.67 [0.50, 0.89]**	
PTx (non-fatal)	**0.17 [0.11, 0.25]**	

[1] Company base case analysis. People were censored 6 months after discontinuation intervention. Estimates adjusted for baseline covariates

Summary of sources used to inform model parameters

Aspect	Data	Source
Background clinical event rates	All-cause mortality by age	Base case: Boer et al. Sensitivity analysis: EVOLVE
	Event rates: CV (initial and repeat); Fx (initial and repeat); & PTx	EVOLVE (placebo arm)
Treatment effects	Proportion achieving >30% PTH reduction	Etelcalcetide trials
	Hazard ratios of clinical events (CV, Fx and PTx)	Base case: EVOLVE Sensitivity analysis: Eandi et al.
Discontinuation	fitted to EVOLVE trial data using Weibull survival function (etelcalcetide and cinacalcet discontinuation assumed to be equivalent)	Base case: EVOLVE Sensitivity analysis: Reams et al. and Urena et al.

Utility values

Utility values	Value	Standard Error or 95% CI	Source
Utility dialysis	0.71	0.013	Briggs et al. 2016 Dolan index
Absolute utility decrements			
Fracture months 1-3	0.31	0.023	Briggs et al. 2016 Dolan index
Fracture after month 3	0.12	0.020	
CV event months 1-3	0.19	0.014	
CV event after month 3	0.14	0.014	
PTx months 1-3	0.06	0.020	
PTx after month 3	-	-	Assumption, based on non-significance (p=0.653)
Calcimimetic treatment	-	-	Conservative assumption, as published point estimate implied a slight utility increase

Costs used in the model

Aspect	Parameters	
Resource use and costs	Drug use and unit costs	Etelcalcetide trials [12-14] BNF and Drug Tariff [49, 50]
	Monitoring frequency and costs	Cinacalcet HTA Reference Costs
	Costs of Fx and CV events	Reference Costs
	Cost of PTx	Pockett et al.: Proton renal database, BNF and Reference costs
	Dialysis frequency and costs	Etelcalcetide trials NICE cinacalcet HTA[2]

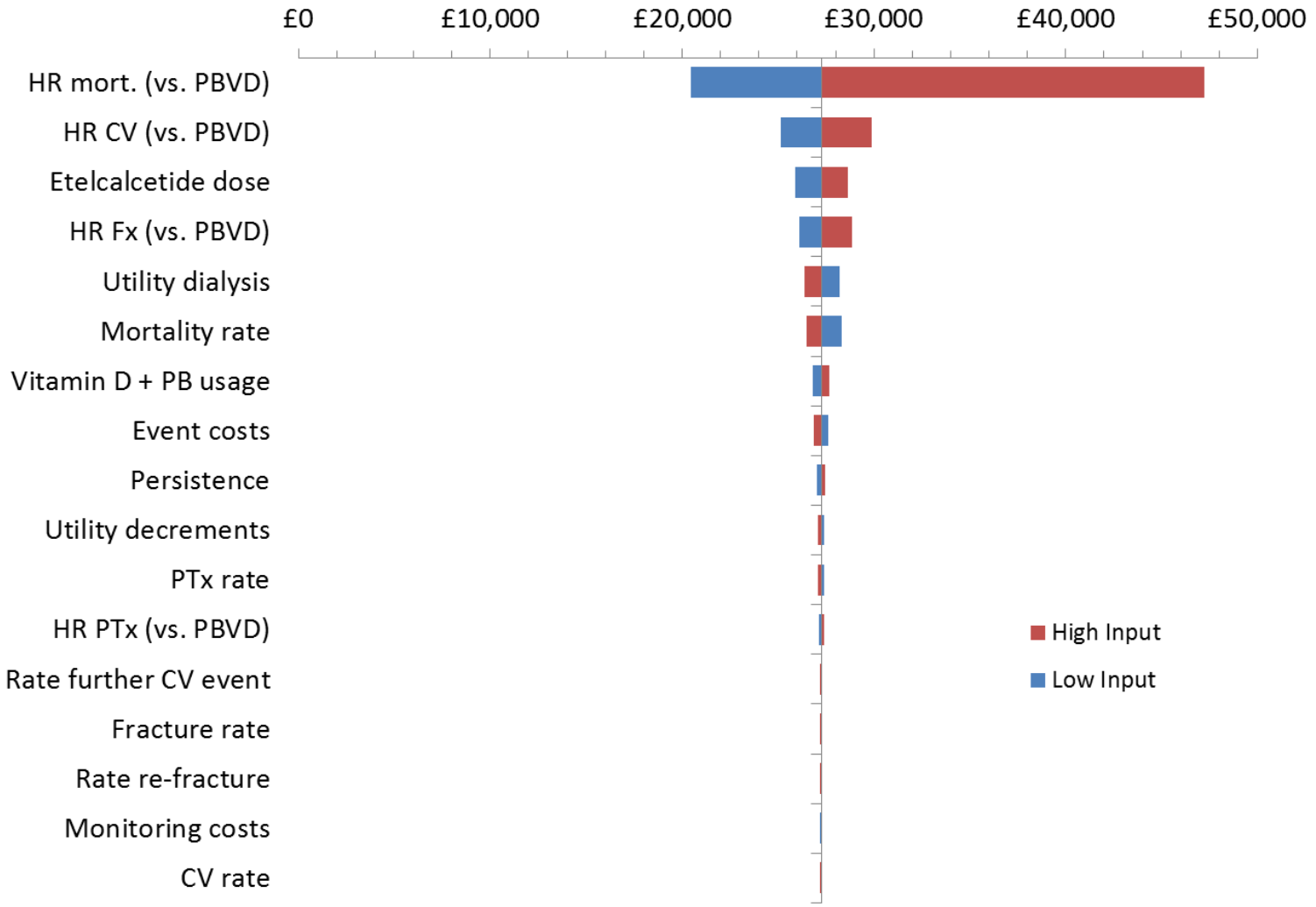
ERG made minor corrections to BNF/tariff prices for drug use and unit costs

Cost effectiveness results – company base case (including PAS)

	Total Costs	Incr. Costs	Total QALYs	Incr. QALYs	ICER (£/QALY)
Broad licensed population (etelcalcetide vs. PB/VD)					
PB/VD	£16,168	-	3.788	-	-
Etelcalcetide*	£24,906	£8,738	4.109	0.321	£27,251
Population with refractory SHPT (etelcalcetide vs. cinacalcet)					
Cinacalcet*	£23,886	-	4.040	-	-
Etelcalcetide*	£24,906	£1,020	4.109	0.069	£14,778

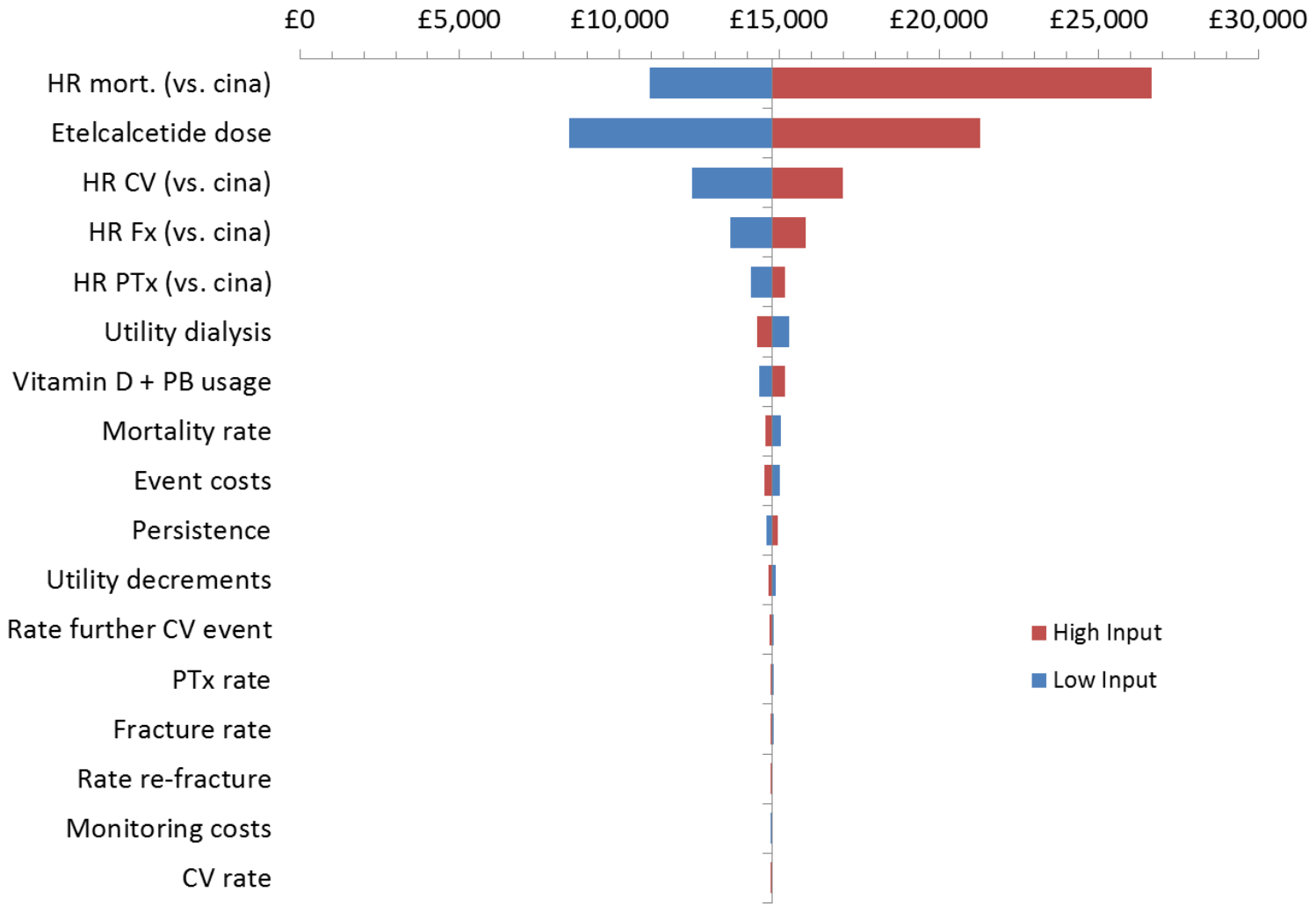
Deterministic sensitivity analysis

Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD



Deterministic sensitivity analysis

Refractory SHPT population – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)



Company scenario analyses (including PAS)

Scenario	ICER	
	Broader population	Refractory SHPT
Base case	£27,251	£14,778
Efficacy: EVOLVE ITT disaggregated	£25,453	£14,623
Efficacy: Eandi; censored	£36,835	£19,334
Efficacy: Eandi; ITT disaggregated	£31,857	£15,975
Age at baseline: 45 years	£28,759	£15,201
Age at baseline: 65 years	£26,160	£14,505
PTx: not included (rate=0)	£28,525	£15,272
Mortality: EVOLVE	£27,490	£14,963
Discontinuation: Reams et al	£25,144	£13,708
Discontinuation: Urena et al.	£27,593	£15,054
Utility: Impact calcimimetic treatment	£23,843	£14,634
Calcimimetic drug use: EAP; head to head	£28,564	£20,880
Dialysis costs: included	£61,280	£48,678
Discount rate: 0%	£23,609	£13,157
Discount rate: 6%	£29,835	£15,938

Reference case – ERG comments

NICE reference case requirements:	**Comment**
Decision problem: As per the scope developed by NICE	The population with refractory SHPT for whom cinacalcet is a comparator was not modelled
Perspective on costs: NHS and PSS	Only acute NHS costs were included; non-acute and PSS costs are omitted
Type of economic evaluation: Cost utility analysis with fully incremental analysis	The company conducted a CUA, but did not present a full incremental analysis
Synthesis of evidence on outcomes: Based on a systematic review	Effect on PTH from naïve pooling of 3 etelcalcetide trials. Other studies of cinacalcet vs PB/VD were not included

ERG comments: effectiveness evidence in model

- Extrapolation from short-term biochemical outcomes in the etelcalcetide trials to patient-relevant outcomes introduces considerable uncertainty over the economic results
- EVOLVE presents best available evidence of long-term effects of calcimimetics, but was subject to imbalance at baseline and high treatment discontinuation and cross-over.
  - ERG acknowledged that the company presented several analyses that attempt to correct for these problems, though it is not clear whether these successfully minimise bias.
- Log-linear method used to extrapolate HRs for etelcalcetide from the EVOLVE is reasonable, but not validated.
- Alternative risk prediction method (Eandi et al) is also not validated.
- Simple pooling of data from the etelcalcetide trials is not appropriate, as it breaks randomisation. This favoured etelcalcetide. ERG would prefer a simple chained indirect comparison (used in ERG base case).

ERG comments

- Parathyroidectomy (PTx) was modelled as an event rather than a health state, so long-term effects and costs (or savings) associated with PTx were excluded. This is likely to favour etelcalcetide.
- Information about the effect of etelcalcetide treatment and related adverse effects on patient utility is lacking. These factors are not included in the economic model
- Costs for CV events and fractures were limited to initial acute treatment. So cost savings associated with better management of SHPT are likely underestimated
- It is unclear whether some model parameters (mortality, CV, fracture and PTx rates, drug doses) are representative for a UK population

ERG additional exploratory analyses
(including PAS)

Scenario	ICER vs PB/VD	ICER vs cinacalcet*
Company base case	£27,251	£14,777
1. Efficacy: simple ITC etelecalcetide trials	£29,730	£23,701
2. Efficacy: ≤ 300 pg/mL simple ITC	£25,373	£11,490
3. Non-adherence adjustment: IPE method	£25,111	£14,292
3. Persistence: 28% at 1 year (Reams et al)	£25,144	£13,707
5. Utility gain (0.02) cinacalcet only	£27,251	£42,761

*Refractory population

ERG exploratory base case analysis (including PAS)

The ERG 'base case' differs from the company base case in two key respects:

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

Treatment strategy	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER £/QALY
Non-refractory to PB/VD alone (8.9% target PTH reduction)					
PB/VD alone	£16,168	3.788			
Etelcalcetide *	£25,046	4.114	£8,879	0.325	£27,290
Refractory to PB/VD alone (8.9% target PTH reduction)					
Cinacalcet *	£24,071	4.070			
Etelcalcetide *	£25,046	4.114	£975	0.044	£22,400

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

ERG subgroup analysis (including PAS)

ERG did a subgroup analysis assuming differing propensity for PTH reduction between the two subgroups:

- 17.1% for non-refractory, based on the ERG meta-analysis of cinacalcet vs placebo trials
- 4.9% target PTH for refractory based on the company's subgroup analysis of etelcalcetide vs. placebo for people who discontinued cinacalcet

Treatment strategy	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER £/QALY
Non-refractory to PB/VD alone (17.1%% target PTH reduction)					
PB/VD alone	£16,168	3.788	-	-	-
Etelcalcetide *	£24,071	4.097	£8,818	0.308	£28,626
Refractory to PB/VD alone (4.9% target PTH reduction)					
Cinacalcet *	£24,071	4.070			
Etelcalcetide *	£25,122	4.135	£1,051	0.065	£16,224

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

Key issues for consideration

- How are patients treated in clinical practice, is NICE guidance on cinacalcet applied?
- Surrogate biochemical outcomes used in the clinical trials of etelcalcitide
  - Data from another trial (of cinacalcet) was used to predict the long term outcomes of survival & incidence of cardiovascular events. Is this reasonable?
- Is the primary outcome of 30% reduction in PTH level and/or a target of 300 pg/ml (or less) appropriate/generalisable to UK clinical practice?
- Was the approach to extrapolating treatment effects appropriate?
  - ERG agreed with log-linear method but company used a ‘naïve’ method of pooling data from the phase III etelcalcetide trials, which ERG considered inappropriate
- ERG highlighted that the relative efficacy of etelcalcetide and cinacalcet in patients wih refractory SHPT unclear
- Company model excluded longer-term savings or health effects that might be associated with parathyroidectomy. Is this appropriate?
- Innovation: IV vs oral therapy

Authors

- **Christian Griffiths**
  Technical Lead
- **Joanna Richardson**
  Technical Adviser
- with input from the Lead Team (Pam Rees, Ellen Rule, Justin Daniels) and the ERG (SHTAC)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Etelcalcetide for treating secondary hyperparathyroidism

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of etelcalcetide within its marketing authorisation for treating secondary hyperparathyroidism in people with chronic kidney disease, receiving haemodialysis.

Background

The parathyroid glands produce parathyroid hormone, which controls the levels of calcium and phosphate in the blood. Excessive production of parathyroid hormone is called hyperparathyroidism and it causes serum calcium levels to increase and serum phosphate levels to fall. Clinical manifestations include deposition of calcium in the blood vessels and the kidneys, pruritus, bone, joint and muscle pain. There is an increased risk of fracture and cardiovascular disease and death, and reduced health-related quality of life.

When hyperparathyroidism is caused by another condition, it is called secondary hyperparathyroidism. Secondary hyperparathyroidism is a common complication of chronic kidney disease. In chronic kidney disease, insufficient filtering of phosphate from the blood in the urine, results in abnormally elevated phosphate levels. High serum phosphate levels can directly and indirectly lead to over activity of the parathyroid glands, leading to the development of secondary hyperparathyroidism.

Secondary hyperparathyroidism may develop in the early stages of chronic kidney disease and almost all people who require renal replacement therapy (dialysis or renal transplantation) have secondary hyperparathyroidism. In 2013, approximately 48,000 people were receiving renal replacement therapy in England including approximately 23,500 receiving haemodialysis[1].

The aim of treatment for secondary hyperparathyroidism is to manage levels of parathyroid hormone, phosphate, and calcium. NICE clinical guideline 157 recommends dietary modification to reduce phosphate intake and the use of phosphate binders to control serum phosphate level in people with advanced chronic kidney disease (stage 4 or 5). Other treatments include hydroxylated vitamin D sterols (calcitriol, alfacalcidol) or the synthetic vitamin D analogue paricalcitol, and modification of the dialysis regimen. In severe hyperparathyroidism, total or partial surgical removal of the parathyroid glands may be needed. NICE technology appraisal guidance 117 does not recommend routine use of cinacalcet in people with end-stage renal disease on maintenance dialysis therapy. It recommends cinacalcet for treating refractory secondary hyperparathyroidism only in those who have plasma

levels of ‘intact parathyroid hormone’ greater than 85 pmol/litre and a normal or high adjusted serum calcium level, and in whom surgical parathyroidectomy is contraindicated.

The technology

Etelcalcetide (brand name unknown, Amgen) is a short peptide that acts on the calcium-sensing receptors present on the hormone producing cells of the parathyroid gland. It acts like calcium (calcimimetic) on the receptors and inhibits parathyroid hormone production and secretion. It is given intravenously.

Etelcalcetide does not currently have a marketing authorisation in the UK for treating secondary hyperparathyroidism. It has been studied in clinical trials, compared with cinacalcet or placebo, for treating secondary hyperparathyroidism in adults with chronic kidney disease receiving haemodialysis. It has also been studied, in a single-arm study, in adults with chronic kidney disease receiving haemodialysis who have higher levels of parathyroid hormone despite having had cinacalcet.

Intervention(s)	Etelcalcetide
Population(s)	People with secondary hyperparathyroidism with chronic kidney disease, receiving haemodialysis
Comparators	• Established clinical practice without calcimimetics (dietary modification to restrict phosphate, phosphate binders, analogues of vitamin D) For people with refractory secondary hyperparathyroidism • Cinacalcet

Outcomes	The outcome measures to be considered include: • survival • incidence of fractures • incidence of cardiovascular events • need for parathyroidectomy • symptoms such as bone pain and itching or mobility • hospitalisation • serum levels of parathyroid hormone • serum levels of calcium and phosphate • health-related quality of life • adverse effects of treatment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy (January 2007). NICE Technology Appraisal 117. Transferred to 'static guidance list' June 2013. Related Guidelines: Chronic kidney disease in adults: assessment and management (July 2014). NICE guideline 182 Chronic kidney disease (stage 4 or 5): management of hyperphosphatemia (March 2013). NICE guideline 157.

	Review date TBC. Related Quality Standards: Renal replacement therapy services for adults (November 2014). NICE quality standard 72. Chronic kidney disease in adults (March 2011). NICE quality standard 5. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: Chronic kidney disease (August 2015) NICE pathway http://pathways.nice.org.uk/pathways/chronic-kidney-disease#content=view-info-category%3Aview-about-menu
Related National Policy	Manual for Prescribed Specialised Services 2013/14 Adult specialist endocrinology services (Chapter 9). Parathyroidectomy http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1a, 1b, 2.1, 2.2. 2.3, and 2.7. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. Rao A, Casula A, Casteldine C (2014) UK Renal Replacement Therapy Prevalence in 2013: National and Centre-specific Analyses, UK Renal Registry 17th Annual Report (Chapter 2): 39-64 https://www.renalreg.org/wp-content/uploads/2014/12/02-Chap-02.pdf (accessed November 2015)

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal (STA)

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

Provisional matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Amgen (etelcalcetide) Patient/carer groups • Black Health Agency • British Kidney Patient Association • Kidney Research UK • Muslim Council of Britain • National Kidney Federation • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Renal Technologists • British Association of Social Workers - Renal Special Interest Group • British Geriatrics Society • British Renal Society • Renal Association • Renal Nutrition Group - British Dietetic Association • Renal Pharmacy Group • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Society of Medicine • UK Clinical Pharmacy Association • UK Renal Pharmacy Group Others • Department of Health • NHS England • Welsh Government • NHS Wirral CCG • NHS Redditch and Bromsgrove CCG	General • Allied Health Professionals • Association of Renal Industries • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Kidney Patients Association • Welsh Urological Society Possible comparator companies • Amgen (cinacalcet) Relevant research groups • Cochrane Renal Group • Cochrane Metabolic & Endocrine Disorders Group • MRC Clinical Trials Unit • National Institute for Health Research • Urology Foundation Associated Public Health Groups • Public Health England • Public Health Wales

Appendix C

Consultees	Commentators (no right to submit or appeal)

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Etelcalcetide for the treatment of secondary hyperparathyroidism [ID908]

Company evidence submission

Amgen Limited

26th October 2016

File name	Version	Contains confidential information	Date
Etelcalcetide_ID908_Amgen Manufacturers Submission_27th January 2017_updated AIC	**1.1**	Yes AIC: Highlighted in yellow and underlined CIC: Highlighted in turquoise and underlined	**27th January 2017**
Etelcalcetide_ID908_Amgen Manufacturers Submission_17th Februay_2017_redacted	**1.2**	Redacted	**17th February 2017**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Summary of Tables

Summary of Figures

Abbreviations

AIC	Akaike's Information Criterion
ASN	American Society of Nephrology
BIA	Budget Impact Analysis
BIM	Budget Impact Model
CBA	Cost Benefit Analysis
CEA	Cost-effectiveness Analysis
CKD	Chronic Kidney Disease
CSR	Clinical Study Report
DOPPS	Dialysis Outcomes and Practice Patterns Study
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
ESRD	End Stage Renal Disease
GEE	Generalised Estimating Equation
GFR	Glomerular Filtration Rate
HCP	Health Care Professional
HES	Health Episode Statistics
HRQL	Health Related Quality of Life
HSUV	Health State Utility Value
ICER	Incremental Cost-effectiveness Ratio
IPCW	Inverse Probability Of Censoring Weights
IPE	Iterative Parameter Estimation
ITT	Intention to Treat
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQOL	Kidney Disease Quality of Life
MBD	Mineral and Bone Disorder
NHS	National Health Service
NNT	Numbers Needed to Treat
PAS	Patient Access Scheme
PB/VD	Phosphate Binders/Vitamin D
PSA	Probabilistic Sensitivity Analysis
PTx	Parathyroidectomy
PTH	Parathyroid Hormone
PVD	Peripheral Vascular Disease
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RPFSTM	Rank Preserving Structural Failure Time Model
SHPT	Secondary Hyperparathyroidism
SLR	Systematic Literature Review
TTO	Time Trade Off
ULN	Upper Limit of Normal
WTP	Willingness to Pay

1 Executive summary

1.1 *Introduction*

Secondary hyperparathyroidism (SHPT) is a serious complication in patients with chronic kidney disease (CKD) on haemodialysis, characterised by persistent elevations in levels of biochemical markers of mineral metabolism, including parathyroid hormone (PTH), calcium, and phosphate [1-3]. It is a progressive condition and, if not adequately controlled, is associated with vascular calcification and bone disease, which elevate the risk of cardiovascular (CV) events, fractures, and premature death [4-7], and reduce quality of life in this patient population [8]. Associated health care costs are high [9, 10]. In England, around 9,000 of the 21,000 patients on haemodialysis are estimated to be affected.

The aim of treatment in SHPT is to maintain PTH, calcium and phosphorus within acceptable target ranges to attenuate these important clinical consequences of SHPT [11]. Standard first-line therapies are phosphate binders and vitamin D regimens (PB/VD), but these often prove insufficient to achieve guideline-recommended levels of these key biochemical parameters, as they often improve one biochemical parameter at the expense of others [12], which may exacerbate SHPT and its complications [13]. In addition, phosphate binders contribute to a high pill burden for these patients, which can lead to poor adherence [14].

In patients refractory to PB/VD, calcimimetic treatment is indicated [11]. A 2007 NICE technology appraisal of cinacalcet, a once daily oral calcimimetic, recommended against its routine use, and instead restricted its use only to those patients with 'very uncontrolled' PTH levels (>800pg/mL) that are refractory to 'standard therapy' [PB/VD regimens] and in who parathyroidectomy is contraindicated [15]. However, the clinical landscape for SHPT has changed over the last 10 years since the NICE technology appraisal of cinacalcet was conducted, and in clinical practice cinacalcet has become an accepted routine treatment for refractory patients beyond the restrictions of the NICE technology appraisal [16]. Cinacalcet as an add-on to PB/VD is significantly more effective than PB/VD alone in such patients, but many still fail to achieve recommended biochemical targets [17], and its effectiveness in practice can be further limited by poor adherence and discontinuations [18, 19].

In patients who still remain uncontrolled on cinacalcet treatment, parathyroidectomy may be indicated [11]. However, parathyroidectomy is an invasive, irreversible surgical procedure that is associated with distinct risks of sustained inappropriately low PTH levels, leading to more complex disease management and associated high costs [20, 21]. As suggested in the internationally respected KDIGO clinical guidelines [11], parathyroidectomy should be considered a treatment of last resort when all medical therapies have been exhausted. Collectively, there are, therefore, clear unmet needs for a more effective alternative treatment option to cinacalcet, that is convenient and does not contribute to the high pill burden for these patients, and that facilitates greater adherence (the taking of doses as prescribed) and persistence (continued treatment) to ensure patients with SHPT can achieve the best possible outcomes from medical therapy.

Etelcalcetide (Parsabiv™) is an innovative intravenous (IV) calcimimetic that represents a significant therapeutic advance in the treatment of SHPT in CKD patients on haemodialysis. When added to PB/VD, etelcalcetide has demonstrated superior, clinically meaningful SHPT control versus PB/VD regimens alone in the broad SHPT population, and also versus the oral calcimimetic cinacalcet when used in addition to PB/VD, irrespective of SHPT severity and prior cinacalcet use. As it is administered intravenously by healthcare professionals at the end of routine haemodialysis, etelcalcetide provides a convenient treatment option for patients with

SHPT that does not contribute to the high pill burden and which may facilitate adherence and persistence, in order to achieve the best possible clinical outcomes.

The cost-effectiveness analyses presented in this submission reflect the NICE scope-defined comparisons of etelcalcetide at its anticipated list price. In its broad licensed indication, etelcalcetide (plus PB/VD) has an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained compared with PB/VD regimens alone. In patients with refractory SHPT, etelcalcetide (plus PB/VD) has an ICER of [redacted] per QALY gained compared with cinacalcet (plus PB/VD). **Amgen has submitted a Patient Access Scheme (PAS) application to the Department of Health, which is under consideration by the PASLU**.

Amgen proposes that etelcalcetide be recommended as a treatment option for patients with SHPT with chronic kidney disease, receiving haemodialysis.

1.2 *Statement of decision problem*

This submission addresses the decision problem as outlined in the final scope issued by NICE [22]. Etelcalcetide is indicated for the treatment of SHPT in adult CKD patients on haemodialysis [23], and is anticipated to be used as an addition to PB/VD regimens, as per its use in clinical trials (see section 4). This submission reflects its positioning for both this broad patient population, for which treatment with PB/VD is the established comparator, and the distinct population of patients with refractory SHPT, for which cinacalcet is the relevant comparator (Table 1). Of note, the final NICE scope does not restrict the comparison against cinacalcet to patients with PTH levels >800pg/mL in who parathyroidectomy is contraindicated (so reflecting the broader established use of cinacalcet in clinical practice). In addition, NICE acknowledges that etelcalcetide will not displace parathyroidectomy, and has excluded parathyroidectomy as a comparator from the final scope [24].

Table 1: Statement of decision problem

	Final scope issued by NICE [22]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with SHPT with chronic kidney disease, receiving haemodialysis	As per final scope	n/a
Intervention	Etelcalcetide	As per final scope	n/a
Comparator (s)	Established clinical practice without calcimimetic (dietary modification to restrict phosphate, phosphate binders, analogues of vitamin D) For people with refractory SHPT: Cinacalcet	As per final scope. Etelcalcetide is anticipated to be used as an addition to phosphate binders and/or analogues of vitamin D, rather than as a replacement for these agents.	n/a
Outcomes	The outcome measures to be considered include: • survival • incidence of fractures • incidence of cardiovascular events • need for parathyroidectomy • symptoms such as bone pain and itching or mobility • hospitalisation • serum levels of parathyroid hormone	Clinical trials: • serum levels of parathyroid hormone • serum levels of calcium and phosphate • health-related quality of life • adverse effects of treatment Economic model: • survival • incidence of fractures	n/a

	Final scope issued by NICE [22]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• serum levels of calcium and phosphate • health-related quality of life • adverse effects of treatment	• incidence of cardiovascular events • need for parathyroidectomy • symptoms such as bone pain and itching or mobility • hospitalisation	
Economic analysis		As per the reference case and final scope	n/a
	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year	Cost effectiveness is expressed in terms of incremental costs per quality-adjusted life years	
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	The time horizon of analysis is life time, to capture all differences in costs or outcomes between the technologies being compared over time	
	Costs will be considered from an NHS and Personal Social Services perspective	Costs are considered from an NHS and Personal Social Services perspective	
Subgroups to be considered	No subgroups are considered in the submission.	As per final scope	n/a
Special considerations including issues related to equity or equality	n/a	n/a	n/a

1.3 *Description of the technology being appraised: Etelcalcetide*

Etelcalcetide is an innovative calcimimetic that is administered intravenously three times per week at the end of routine haemodialysis sessions, providing healthcare professionals with complete control over its administration. It binds to and activates the calcium-sensing receptor (CaSR), at a site which is distinct from the sites activated by calcium and the daily oral calcimimetic cinacalcet [25, 26], to reduce secretion of PTH. The reduction in PTH is associated with a concomitant decrease in serum calcium and phosphate levels.

Etelcalcetide has demonstrated superiority in lowering PTH versus cinacalcet, allowing more patients to reach SHPT goals. A positive CHMP opinion for etelcalcetide, for the treatment of SHPT in adult patients with CKD on haemodialysis, was received in September 2016 [27](Table 2).

Table 2: Description of technology being appraised

UK approved name and brand name	Parsabiv™ (Etelcalcetide)
Marketing authorisation	CHMP positive opinion received 15 September 2016. EMA approval anticipated November 2016.

Indications and any restriction(s) as described in the summary of product characteristics	Etelcalcetide is indicated for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis [23]. Corrected serum calcium should be at or above the lower limit of the normal range prior to administration of the first dose, a dose increase, or re-initiation after a dose stop. Etelcalcetide should not be administered more frequently than 3 times per week.
Method of administration and dosage	Etelcalcetide is administered three times per week by bolus injection into the venous line of the dialysis circuit at the end of routine haemodialysis treatment during rinse back or intravenously after rinse back. The starting dose is 5mg, with titration (up or down) in 2.5mg to 5mg increments no more frequently than every 4 weeks. Dose should be individualised in the range 2.5mg to 15mg three times per week [23].

1.4 *Summary of the clinical effectiveness analysis*

A systematic literature review confirmed the three large, 26-week, phase 3, double-blind, etelcalcetide randomised controlled trials (RCTs) included in the European marketing authorisation application provide the relevant clinical data to address the decision problem outlined in the NICE scope (see section 4.1). These include two placebo-controlled trials that enrolled patients with baseline PTH >400pg/mL (studies 20120229 and 20120230) [28, 29], and had near-identical designs that allowed an integrated analysis of both efficacy and safety. The third trial directly compared etelcalcetide against cinacalcet in patients with baseline PTH >500pg/mL (study 20120360), which was powered to detect both non-inferiority and superiority [30].

All three trials evaluated etelcalcetide and the comparators when added to a background of therapies including phosphate binders and vitamin D, in line with their expected use in practice (see section 4.3). Treatment was targeted towards achieving PTH ≤300pg/mL, and in all three trials the primary endpoint was achievement of >30% reduction from baseline in mean PTH during the efficacy assessment phase (EAP, weeks 20-27). Achievement of >30% reduction in PTH was the primary endpoint in registration studies for vitamin D sterols, was a secondary endpoint in the registration studies for cinacalcet, and was noted by the CHMP to be relevant and clinically meaningful in SHPT [25].

1.4.1 Clinical efficacy

In both placebo-controlled RCTs individually, and in an integrated analysis, etelcalcetide was statistically superior to placebo for the primary endpoint of >30% reduction from baseline in mean PTH during the efficacy assessment phase (EAP, weeks 20-27) (integrated analysis: 74.7% vs. 8.9%; Odds ratio [OR] [95% CI]: 31.60 [21.59 to 46.25]; P<0.001; number needed to treat [NNT]: 2) (Table 3). Consistent with the primary endpoint, etelcalcetide was statistically superior for all pre-specified secondary endpoints, including the proportion of patients with mean PTH ≤ 300 pg/mL, percent decreases from baseline in mean PTH, corrected calcium (cCa), corrected calcium-phosphate product (cCa x P) and phosphorous (P) during the EAP compared with placebo (P<0.001) [31] (section 4.7.2).

Table 3. Primary and key secondary PTH endpoint results in placebo-controlled RCTs

Endpoints	Pooled placebo-controlled RCTs (20120229 & 20120230)	
	Placebo (n=514)	Etelcalcetide (n=509)
Achievement of >30% reduction in PTH during EAP, n(%)	46 (8.9)	380 (74.7)
	OR (95% CI): 31.60 (21.59, 46.25) P<0.001	
Achievement of PTH <300pg/mL during EAP, n(%)	25 (4.9)	262 (51.5)
	OR (95% CI): 27.02 (16.62, 43.93); P<0.001	
EAP, efficacy assessment phase (weeks 20-27)		

In the active-controlled RCT, etelcalcetide met the criteria for non-inferiority against cinacalcet for the primary endpoint of the proportion of patients with a >30% reduction from baseline in mean PTH during the EAP, and was statistically superior to cinacalcet for the key secondary endpoints of proportion of patients with a > 50% reduction from baseline in mean PTH during the EAP (52.4% vs 40.2%; OR [95% CI]: 1.65 [1.21, 2.23]; P=0.001; NNT:8) and the proportion of patients with a > 30% reduction from baseline in mean PTH during the EAP (68.2% vs 57.7%; OR [95% CI]: 1.59 [1.16, 2.17]; P=0.004; NNT: 10) (Table 4, and section 4.7.3).

Table 4. Primary and key secondary PTH endpoint results in active-controlled RCT

Endpoints	Active-controlled RCT (20120360)	
	Cinacalcet (n=343)	Etelcalcetide (n=340)
Achievement of >30% reduction in PTH during EAP, n(%)*	198 (57.7)	232 (68.2)
	OR (95% CI): 1.59 (1.16, 2.17) P=0.004	
Achievement of >50% reduction in PTH during EAP, n(%)	138 (40.2)	178 (52.4)
	OR (95% CI): 1.65 (1.21, 2.23) P=0.001	
EAP, efficacy assessment phase (weeks 20-27) *Secondary endpoint superiority testing after meeting primary non-inferiority for same endpoint		

In all three trials, the superior efficacy of etelcalcetide over the comparators was consistent across all pre-defined patient subgroups based on demographics, severity of SHPT and use of prior cinacalcet therapy [28-30], indicating that etelcalcetide is similarly effective across all types of the broad range of patients with SHPT seen in clinical practice, including those representative of refractory SHPT patients (section 4.8). Supporting open-label extension studies, providing up to 18 months of follow-up data for patients enrolled in RCTs, show that the efficacy of etelcalcetide is maintained with long-term treatment [32, 33] (section 4.11.2).

1.4.2 Clinical safety

Three phase 3 RCTs providing safety data for up to 26 weeks (n=841 etelcalcetide, n=513 placebo, n=341 cinacalcet), and open-label extension studies following patients for up to 18 months, confirm that etelcalcetide is well tolerated, and has an AE profile consistent with the pre-existing comorbid conditions typically associated with SHPT in patients with CKD on haemodialysis and the mechanism of action of calcimimetics. Adverse events (AEs) that occurred in RCTs with a numerically greater frequency in the etelcalcetide group (≥ 5% in the etelcalcetide group with ≥ 1% difference from placebo or cinacalcet) related to decreases in serum calcium levels, most of which were asymptomatic. Symptomatic hypocalcaemia occurred in 7.0% on etelcalcetide vs. 0.2% on placebo, and in 5.0% on etelcalcetide vs. 2.3% on cinacalcet, but these were mild or moderate in severity; no serious AEs of hypocalcaemia

were reported in any of the three RCTs [34] (section 4.12). No new safety concerns were identified in open-label extension studies of up to 18 months of treatment with etelcalcetide [32, 33] (section 4.12.2).

1.4.3 Key strengths and limitations of the clinical data

The three phase 3 etelcalcetide RCTs enrolled a population of haemodialysis patients with SHPT who are broadly representative of the patients anticipated to use etelcalcetide in clinical practice. This included patients who were calcimimetic-naïve, and patients with prior cinacalcet use suggesting a history of being refractory to PB/VD regimens alone. The RCTs employed etelcalcetide and comparator treatment regimens and dosing algorithms as they would be used in clinical practice, and they assessed outcomes that are relevant to the management of SHPT in clinical practice and were considered clinically meaningful by the CHMP [25]. Results are consistent, biologically plausible, and highly relevant to clinical practice. Formal quality assessment indicates the results are robust and at low risk of bias. As such, these data effectively address the decision problem outlined in the final NICE scope.

It is possible that treatment to a target PTH $\leq$300pg/mL may have resulted in higher drug dosing in the trials than would be used in clinical practice, where PTH targets are less stringent [11]. Discontinuation of cinacalcet was also lower in the active-controlled trial than is typically observed in clinical practice [19, 35, 36], which may have led to an underestimate of the relative treatment effects of etelcalcetide compared with cinacalcet. A potential limitation is that the trials assessed biochemical endpoints, rather than clinical events such as fracture, CV events and deaths. However, as accepted by NICE in its appraisal of cinacalcet, the link between elevated PTH and the risk of clinical events is well established [15], and the biochemical parameters used to evaluate etelcalcetide effectiveness in these trials are those used in clinical practice to guide therapeutic decisions in the management of SHPT (section *3.1.2.1*).

1.5 Summary of the cost-effectiveness analysis

1.5.1 De novo economic model

The economic analysis is based on a *de novo* life-time Markov model that includes health states reflective of the clinical consequences of SHPT: non-fatal CV events, fractures and all-cause mortality. Patients move between these states based on modelled event rates with the treatment received. Those on calcimimetic may remain on calcimimetic or discontinue to phosphate binder and vitamin D. In line with the final NICE scope, etelcalcetide is compared against therapy with PB/VD within its wide licensed indication, and against cinacalcet in patients with refractory SHPT [22]. As these are distinct populations, pairwise analysis, rather than a fully incremental analysis, is appropriate.

In order to model clinical event rates for etelcalcetide, the proportion of patients meeting the primary endpoint of the etelcalcetide trials have been extrapolated, via a log-linear relationship, to the hazard ratios for these clinical events observed with calcimimetic in the large outcomes-based EVOLVE trial. Although the primary intention-to-treat (ITT)-based analysis of EVOLVE did not favour cinacalcet over placebo, pre-specified analyses adjusting for imbalances in baseline characteristics and accounting for time on treatment demonstrate cinacalcet significantly reduced CV events, mortality and fractures [37, 38]. Hazard ratios for these events based on such analyses were therefore used in the base case model. An alternative approach of modelling outcomes, based on a published biomarker risk prediction scheme [39], has also been used in scenario analyses. Utility values are derived from the

EVOLVE trial, and detailed resource use and costs are informed by the literature and current unit costs.

Based on its anticipated list price, the lifetime, discounted incremental costs per QALY gained with etelcalcetide (plus PB/VD) vs. PB/VD alone and etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) are presented in Table 5 and Table 6, respectively.

Table 5: Pairwise incremental cost per QALY gained (discounted) – broad licensed population

	Total Cost	Δ Cost	Total QALYs	Δ QALYs	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	4.109	-	[redacted]
PB/VD	[redacted]	[redacted]	3.788	0.321	[redacted]

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

Table 6: Pairwise incremental cost per QALY gained (discounted) – refractory SHPT

	Total Cost	Δ Cost	Total QALYs	Δ QALYs	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	4.109	-	[redacted]
Cinacalcet*	[redacted]	[redacted]	4.040	0.069	[redacted]

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

Deterministic sensitivity analyses indicate the model is most sensitive to the relative effects of etelcalcetide on mortality and, to a lesser extent, CV and fracture events. However, probabilistic sensitivity analysis produces ICER estimates that are highly consistent with the deterministic base case analysis, and scenario analyses modelling clinical outcomes via a published biomarker risk prediction scheme produce similar cost, QALY and ICER estimates to those in the base case.

A PAS application, proposing a confidential, simple discount on the list price for etelcalcetide, has been submitted to the Department of Health. ICER estimates based on this discounted etelcalcetide price will be presented as an addendum.

1.5.2 Key strengths and limitations of the cost effectiveness data

The de novo economic model fulfils the requirements of the NICE reference case and addresses the final NICE scope. In the absence of directly assessed clinical outcomes data for etelcalcetide, the most robust endpoint data from the etelcalcetide trials have been extrapolated to hazard ratios for clinical events derived from the most robust source of calcimimetic outcomes. To verify the appropriateness of this approach, a published biomarker risk algorithm was also used to model clinical outcomes, which produced ICER estimates consistent with those in the base case. NICE has acknowledged the relationship between biochemical parameters and clinical outcomes in SHPT, and accepted the evidence review group's approach to modelling clinical outcomes based on PTH levels in the 2007 Technology Appraisal of cinacalcet [15]. The model is therefore considered to provide robust estimates of the cost effectiveness of etelcalcetide.

1.6 *Summary conclusions*

Etelcalcetide is an innovative IV calcimimetic, which represents a significant therapeutic advance in the treatment of SHPT in CKD patients on haemodialysis. It has robustly

demonstrated clinically meaningful and superior SHPT control over placebo and cinacalcet when added to PB/VD across the broad population of SHPT patients meeting its licensed indication, and in specific subgroups within this, including those with SHPT that is refractory to PB/VD alone. Etelcalcetide is well tolerated with an adverse event profile consistent with the pre-existing comorbid conditions typically associated with SHPT and the mechanism of action of calcimimetics. This favourable benefit:risk profile is maintained with long-term treatment.

Coupled with its IV administration, which places control of administration in the hands of health care professionals at the end of dialysis sessions, etelcalcetide has the potential to address the significant unmet needs for a more effective and convenient medical treatment option that does not contribute to the high pill burden, and which may facilitate adherence and persistence in order to achieve the best possible clinical outcomes for patients with SHPT.

The cost-effectiveness analyses presented in this submission reflect the NICE scope-defined comparisons of etelcalcetide at its anticipated list price. In its broad licensed indication, etelcalcetide (plus PB/VD) has an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained compared with PB/VD regimens alone. In patients with refractory SHPT, etelcalcetide (plus PB/VD) has an ICER of [redacted] per QALY gained compared with cinacalcet (plus PB/VD). Amgen proposes that etelcalcetide be recommended as a treatment option for patients with SHPT with chronic kidney disease, receiving haemodialysis.

2 The technology

2.1 *Description of the technology*

Brand name

Parsabiv™

Approved name

Etelcalcetide

Therapeutic class

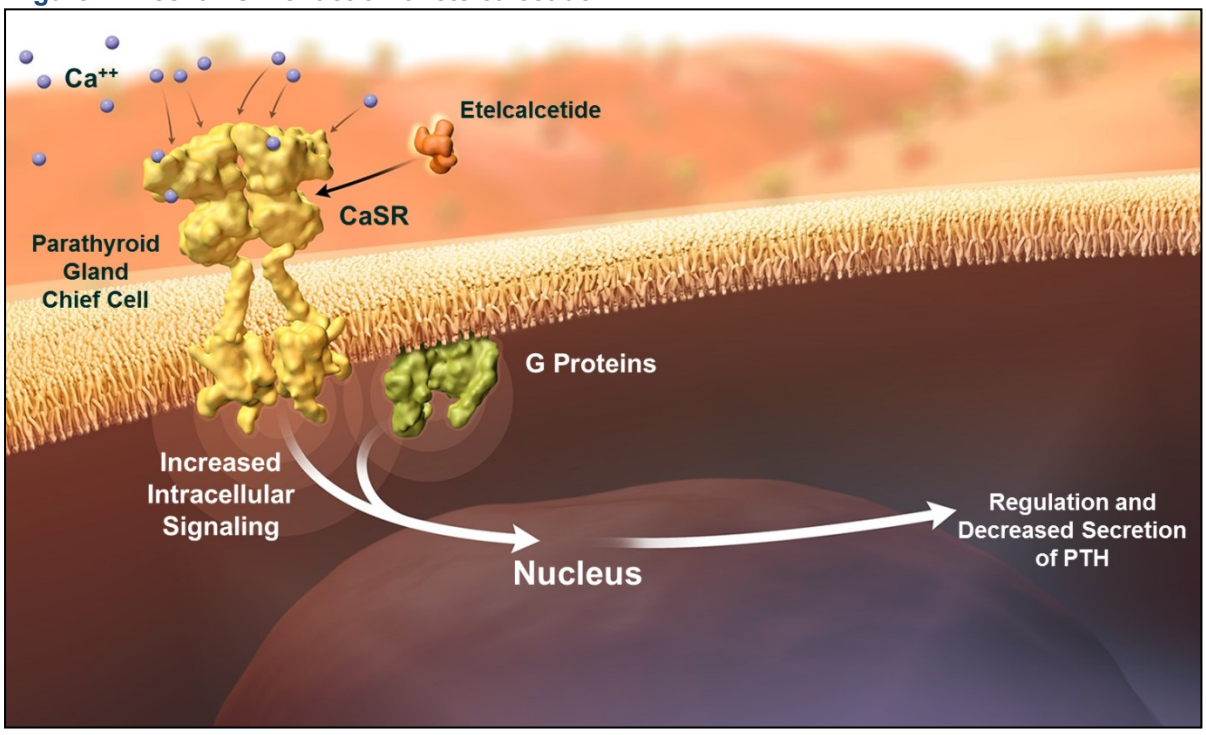
Calcium homeostasis, anti-parathyroid agents. ATC code: H05BX04

Mechanism of action

Etelcalcetide is an innovative, intravenous (IV) calcimimetic agent that binds to and activates calcium-sensing receptors (CaSR) located in the parathyroid glands, thereby reducing secretion of parathyroid hormone (PTH) (Figure 1). The reduction in PTH is associated with a concomitant decrease in serum calcium and phosphate levels.

Etelcalcetide is an allosteric activator of the CaSR, binding directly to the extracellular domain and activating the receptor at a site which is distinct from the sites activated by calcium and the daily oral calcimimetic cinacalcet [25, 26]. It is the only calcimimetic agent formulated for IV administration.

Figure 1: Mechanism of action of etelcalcetide



CaSR, calcium sensing receptor; PTH, parathyroid hormone

2.2 Marketing authorization and health technology assessment

2.2.1 UK Marketing authorisation and licensed indication

Etelcalcetide received a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) on 15 September 2016, "…*for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy"* [27]. Regulatory approval across the EU is anticipated in [redacted], and the product will be available for use of after the granting of MA. Etelcalcetide is not yet licensed or launched in any other jurisdictions.

The draft EU Summary of Product Characteristics (SmPC) is attached as Appendix 1. This notes that etelcalcetide is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. In addition, etelcalcetide should not be initiated if corrected serum calcium is less than the lower limit of the normal range [23].

The draft CHMP assessment report is attached as Appendix 2. No issues were identified by CHMP with respect to the design, conduct or results of the etelcalcetide clinical trials. The phase 3 RCTs were considered to have enrolled appropriate patients and to have evaluated relevant etelcalcetide and comparator drug regimens using clinically relevant efficacy and safety of endpoints. Long-term studies were considered reassuring. The main etelcalcetide adverse events discussed in the report relate to decreases in serum calcium concentrations and their sequelae. These are noted to be related to the known mechanism of action of calcimimetics, were mainly mild-to-moderate in severity, and were manageable by the clear, flexible dosing algorithms used in the trials and reflected in the SmPC, and rarely led to permanent discontinuation of etelcalcetide. No specific conditions beyond the usual requirements for pharmacovigilance activities and periodic safety update reports are attached to the recommended marketing authorisation [25].

2.2.2 UK HTA

Etelcalcetide will be subject to appraisal by the Scottish Medicines Consortium (SMC) in accordance with its remit to assess newly licensed medicines. We anticipate making an SMC submission for etelcalcetide in Q1 2017, and anticipate publication of advice in accordance with their timelines and submission scheduling process.

2.3 Administration and costs of the technology

A brief overview of the administration and costs of etelcalcetide is provided in Table 7.

An application for a simple PAS providing a confidential discount on the anticipated list price for etelcalcetide has been submitted to the Department of Health.

Table 7: Costs and administration of etelcalcetide

Feature of etelcalcetide treatment		Source
Pharmaceutical formulation	2.5 mg solution for injection 5 mg solution for injection 10 mg solution for injection All presented in single-use glass vials.	Draft SmPC [23] (See Appendix 1)
Acquisition cost (excluding VAT) *	[redacted]	
Method of administration	Etelcalcetide is administered by bolus injection into the venous line of the dialysis circuit at the end of routine haemodialysis treatment during rinse back or intravenously after rinse back	Draft SmPC [23] (See Appendix 1)
Doses	The starting dose is 5mg three times per week. Doses should be titrated up or down so that doses are individualized between 2.5 mg and 15 mg three times per week. Dose increases should be made in 2.5mg to 5mg increments no more frequently than every 4 weeks.	Draft SmPC [23] (See Appendix 1)
Dosing frequency	Etelcalcetide is administered three times per week during routine haemodialysis sessions	Draft SmPC [23] (See Appendix 1)
Average length of a course of treatment	Given the chronic nature of SHPT in CKD patients on haemodialysis, etelcalcetide treatment is anticipated to be ongoing	
Average cost of a course of treatment	n/a	
Anticipated average interval between courses of treatments	n/a	
Anticipated number of repeat courses of treatments	n/a	
Dose adjustments	Etelcalcetide should be titrated up or down to individualised doses between 2.5 mg and 15 mg. PTH should be measured after 4 weeks from initiation or dose adjustment of etelcalcetide to determine the need for dose adjustment. The dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target PTH. Dose adjustments based on PTH levels and serum calcium levels are extensively detailed in the SmPC.	Draft SmPC [23] (See Appendix 1)
Anticipated care setting	Tertiary setting – renal units	

2.4 *Changes in service provision and management*

Etelcalcetide will be commissioned by NHS England as part of specialist renal services. Administration will be by health care professionals in renal / dialysis units during routine haemodialysis sessions. Etelcalcetide is anticipated to be used as part of a therapeutic regimen including PB/VD.

Renal units provide specialist staffing and infrastructure for the wide range of therapies that CKD patients on haemodialysis require, and no reconfiguration of any related services will be required. It is not anticipated that etelcalcetide will result in significant additional resource use for administration, and the SmPC recommendations for monitoring laboratory parameters such as PTH and calcium are the same as those recommended for cinacalcet [23, 40].

2.5 *Innovation*

Chronic kidney disease (CKD) patients on haemodialysis face one of the highest daily pill burdens of all chronic diseases [41]. Adherence to prescribed oral medications is a widely recognised problem in these patients due to the complexity of regimens and the lifelong duration of the therapy [18]. Cinacalcet is a daily oral calcimimetic treatment that in clinical trial settings has demonstrated clinically meaningful and sustainable improvements in PTH, calcium, and phosphate levels in patients with SHPT [17]. However, cinacalcet may not deliver optimal therapy in clinical practice due to poor patient adherence with oral therapy and high discontinuation rates (up to 59% at 12 month post initiation in European settings) [35, 36]. Survival in this population has been shown to be reduced with cinacalcet treatment discontinuation compared with treatment persistence [42].

Etelcalcetide is an innovative calcimimetic that acts on the CaSR at a site distinct from that of calcium and cinacalcet. It is the only calcimimetic formulated for IV administration, and is administered three times per week at the end of routine haemodialysis sessions [23]. As healthcare professionals have complete control over its administration, this may improve adherence and persistence with calcimimetic therapy compared with daily oral cinacalcet therapy, and so facilitate better control of SHPT.

A 26-week, head-to-head, phase 3 RCT observed superior SHPT control with etelcalcetide despite no difference in persistence compared with cinacalcet [30]. However, persistence with cinacalcet was >80% in this 26-week trial, which is substantially greater than the persistence typically observed with cinacalcet in clinical practice [19, 35, 36], likely due to the clinical trial setting. Therefore, the trial-based relative treatment effects of healthcare professional-administered etelcalcetide vs. daily oral, patient-administered cinacalcet may be underestimated compared with effects that may be seen in clinical practice.

NICE clinical guidelines on the management of CKD [43] and KDIGO clinical practice guidelines [11] support the involvement of patients in decision-making and consideration of their preferences when initiating treatment plans in CKD. [redacted][44][redacted]

[redacted][16][redacted]

In summary, etelcalcetide is an innovative new therapy that provides a step change in the treatment of SHPT based on its superior efficacy and IV formulation that provides healthcare professionals with complete control over its administration. The quality-adjusted life years (QALYs) estimated in the economic model (section 5) are based on the phase 3 RCT data, and are likely to underestimate the relative treatment effects of etelcalcetide compared cinacalcet when used in clinical practice. Furthermore, the QALY estimates do not capture the convenience and confidence derived from healthcare professional-administered IV etelcalcetide, which drives patient and clinician preferences for this therapy.

3 Health condition and position of the technology in the treatment pathway

Summary

- SHPT is a serious complication of CKD. Of the 21,000 patients on haemodialysis in England, around 9,000 are estimated to have SHPT.
- SHPT is a progressive condition, characterised by persistent elevations in levels of biochemical markers of mineral metabolism, including parathyroid hormone (PTH), calcium, and phosphate. If not adequately controlled, it is associated with vascular calcification and bone disease, which increase the risk of cardiovascular (CV) events, fractures, and premature death, and reduce quality of life in this patient population.
- Current medical treatment of SHPT begins with phosphate binders to reduce serum phosphate levels, and vitamin D sterols to reduce PTH levels; however, control of one biochemical parameter with use of these agents is often achieved at the expense of control of other parameters, which may exacerbate SHPT and its complications. In addition there are significant challenges in adherence to these agents due to high pill burden and tolerability issues.
- Cinacalcet, a once daily oral calcimimetic, is established in England as a treatment for refractory SHPT that is used routinely beyond the very restricted recommendation for its use in a NICE Technology Appraisal in 2007.
- Cinacalcet as an add-on to PB/VD is significantly more effective than PB/VD alone in such patients, but many still fail to achieve recommended biochemical targets, and its use in clinical practice is limited by issues of poor adherence and high discontinuations.
- Parathyroidectomy is an invasive, irreversible surgical procedure that is associated with distinct risks of sustained inappropriately low PTH levels, leading to more complex disease management and associated high costs. It is considered a treatment of last resort when all medical therapies have been exhausted.
- There are clear unmet needs for a more effective alternative treatment option to cinacalcet, that is convenient and does not contribute to the high pill burden for these patients, and that facilitates greater adherence (the taking of doses as prescribed) and persistence (continued treatment) to ensure patients with SHPT can achieve the best possible outcomes from medical therapy.
- Etelcalcetide is a novel, long-acting intravenous (IV) calcimimetic that can address these unmet needs.
  - Etelcalcetide has demonstrated superior, clinically meaningful SHPT control over placebo and cinacalcet when all are added to PB/VD. It has an adverse event profile similar to cinacalcet (see section **Error! Reference source not found.**).
  - Etelcalcetide is administered three times per week at the end of routine haemodialysis sessions, providing healthcare professionals with complete control over its administration, which may facilitate improved adherence and persistence compared with daily oral therapy.
- Etelcalcetide has a positive CHMP opinion for the 'treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy' and will be indicated across the broad population of patients with SHPT, irrespective of disease severity and prior therapy.

3.1 *Overview of SHPT in CKD patients on haemodialysis*

3.1.1 SHPT background information

SHPT is a serious complication of chronic kidney disease (CKD) that is characterised by elevated levels of serum parathyroid hormone (PTH), disturbances in calcium and phosphate, and abnormalities in bone and mineral metabolism [1, 2].

The kidneys play an integral role in the homeostasis of calcium and phosphate levels, and vitamin D metabolism [13]. In patients with CKD, these mechanisms are impaired. Development of SHPT among these patients represents an early adaptive response that serves initially to maintain calcium homeostasis as kidney function declines. Alterations in calcium and phosphate regulation lead to a reduction in signaling through the calcium-sensing receptor and an increase in PTH secretion. PTH maintains calcium levels by modifying the release of calcium and phosphorus into the blood from the bone. Elevations in phosphorous levels are controlled through a compensatory decrease in the rate of renal tubular reabsorption, leading to greater excretion of phosphorus, also mediated by PTH. However, when renal function deteriorates further towards end stage renal disease, PTH cannot increase phosphorus excretion further and hyperphosphatemia develops. Hyperphosphatemia continues to stimulate PTH secretion, leading to parathyroid gland hyperplasia and further PTH secretion. Hyperphosphatemia also inhibits the renal tubular enzymes responsible for activating vitamin D, leading to vitamin D deficiency, which reduces calcium absorption from the gastrointestinal tract and further contributes to elevations in PTH levels [1, 2] [13].

The result is progressive, uncontrolled increases in PTH levels, which lead to abnormalities in bone and mineral metabolism. Important clinical consequences include pathological changes in bone and vascular calcification, which can increase the risk of skeletal fracture, cardiovascular (CV) events and death [13, 45, 46].

3.1.2 Patient burden

3.1.2.1 Increased risks of clinical events and mortality

SHPT leads to CKD-mineral and bone disorder (CKD-MBD) [47], which causes bone and joint pain, reductions in bone mass, and an increased risk of skeletal fracture [2, 48]. High PTH levels contribute to the higher risk of fractures in ESRD patients: in the Dialysis Outcomes and Practice Patterns Study (DOPPS), PTH levels > 900 pg/mL were associated with a 72% higher risk of fractures compared with PTH in the controlled range of 150 to 300 pg/mL [6]. Higher fracture risk was also reported in patients with elevated alkaline phosphatase, an important bone health marker related to SHPT [49].

Disturbances in calcium and phosphorus metabolism in SHPT are also thought to contribute to calcification of soft tissues and the vasculature [2], which may contribute to increased rates of CV events and mortality in dialysis patients [50-52]. Several large observational studies have consistently reported the association of high PTH, calcium, and phosphate with mortality [4, 5, 7, 45, 46, 53, 54]. For example, an analysis of DOPPS data from 35,655 dialysis patients followed over 15 years (1996-2011) observed that, compared with a PTH level of 150–300 pg/mL, in adjusted models, all-cause mortality risk was higher for PTH=301–450 (hazard ratio, 1.09; 95% confidence interval, 1.01 to 1.18) and PTH>600 pg/mL (hazard ratio, 1.23; 95%

confidence interval, 1.12 to 1.34). PTH >600 pg/ml was also associated with higher risk of CV mortality as well as all-cause and CV hospitalisations [46]. When adjusted for patient characteristics and disease history, uncontrolled PTH levels, in addition to calcium and phosphorous, appear to have a central role in the development of SHPT-related morbidity and SHPT-related mortality.

Further support of the role of PTH in SHPT-related morbidity and mortality can be found in the change in the clinical course of SHPT when PTH, along with other biomarkers, is more effectively controlled. A cohort study by Danese et al [55] observed that simultaneous control of PTH, calcium, and phosphate was associated with increased survival compared with control of one or two of these parameters; similarly, long-term consistent control of these biomarkers was associated with better survival than episodic control. In addition, compelling evidence of the specific role of PTH is also available from the large EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) RCT, which when adjusted for important confounding factors, observed cinacalcet, a potent inhibitor of PTH secretion, reduced the risks of all-cause mortality and major CV events when added to background phosphate binder and vitamin D sterols [37, 56] (see section 3.3.2.1).

In summary, retrospective observational data and prospective clinical trial data consistently indicate that development of SHPT is associated with a range of adverse clinical events, including fractures, CV events and death, in haemodialysis patients. Uncontrolled PTH, along with calcium and phosphate levels, has a central role in the development and risk of these events, as demonstrated by significant reductions in the risks of these events when PTH levels are controlled effectively.

3.1.2.2 Reduced health-related quality of life

Fractures and CV events arising from SHPT have short-term and long-term negative consequences on health-related quality of life. Clinical trial data indicate an overall mean EuroQoL (EQ)-5D score of 0.74 in SHPT patients, which was reduced by fractures (mean EQ-5D = 0.35 during the 3 months post-event) and CV events (mean EQ-5D = 0.48 in the 3 months post event) [57]. Another study, using direct preference-based utility elicitation methods in the general public, reported similarly profound effects of SHPT-related events on quality of life [58].

Although many patients with SHPT are not overtly symptomatic, bone pain is common. Frequent additional symptoms include aching and stiffness of the joints, muscle soreness, dry skin, and pruritus [59]. Dialysis patients with elevated PTH have been demonstrated to have reduced physical functioning and increased pain [8], and abnormal phosphate (both high and low), as well as low PTH is shown to be associated with reduced self-reported physical functioning [60].

3.1.3 Epidemiology of SHPT

3.1.3.1 Prevalence and incidence

Estimates of the prevalence of SHPT vary depending on the definition of SHPT used. The NICE Scope for this appraisal reports that almost all people who require renal replacement therapy (dialysis or renal transplantation) have secondary hyperparathyroidism [22]. In contrast, based on a definition of PTH levels >300pg/mL, the DOPPS study reported a prevalence of SHPT for the UK of 41.4% of the dialysis population based on data from 2011 [61], and a systematic literature review of the burden of SHPT in CKD patients reported a prevalence of 42.9% of the haemodialysis population in the UK using DOPPS data from 2010

[3]. Applying this higher figure to the number of haemodialysis patients estimated from UK Renal Registry data [62], would suggest around 9,000 of the 21,000 patients on haemodialysis in England have SHPT.

The prevalence of haemodialysis is increasing at a rate of around 1% per year in the UK [62], and internationally the percentage of ESRD patients with PTH levels >300pg/mL has increased continually over the 15-year period from 1996 to 2011 [46]; however, this latter finding may be influenced by the revisions to PTH targets from the stringent K/DOQI guideline recommendations of 2 to 4 times the upper limit of normal, to the current KDIGO guideline recommendation of 2 to 9 times the upper limit of normal [11].

3.1.3.2 Risk factors

The majority of ESRD patients develop SHPT. However, age and dialysis vintage (i.e. time since dialysis was required to manage CKD) are important factors correlating with elevated PTH [63]. In addition, the US SEEK study [64], reported gender, diabetes, body mass index, and eGFR as independent risk factors for SHPT. In this study, black CKD patients had a 2.9-fold greater risk of SHPT (95% CI: 1.9 to 4.4) compared with non-black patients.

3.1.4 Economic burden

The economic burden of SHPT in the dialysis population is substantial. A retrospective study in several European countries showed that uncontrolled SHPT was associated with increased health resource utilisation and costs [9]. Elevated levels of PTH, phosphate, and to a lesser extent calcium, were associated with a greater intensity of healthcare resource utilisation (as measured by medications and SHPT-related hospitalisations due to CV disease, fracture, and parathyroidectomy) and higher direct medical costs. The SHPT-related hospitalisation rate was 6.6 per 100 patient-years, with a higher rate observed for patients with baseline PTH > 600 pg/mL compared to those with lower PTH. Likewise, total monthly healthcare costs were on average 11% higher for patients with baseline PTH between 300 and 600 pg/mL and 41% higher for patients with baseline PTH > 600 pg/mL compared with those in the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommended range of 150 to 300 pg/mL [9]. Improving SHPT control across the whole range of PTH thresholds therefore has the potential to reduce SHPT-related healthcare resource utilisation (medications and SHPT-related hospitalisations due to CV disease, fracture, and parathyroidectomy) and costs.

3.2 Current treatment guidelines for SHPT

3.2.1 Overview of clinical guidelines relevant to UK

Table 8 summarises current clinical guidelines related to the management of SHPT of relevance to UK clinical practice. These are discussed in the sections that follow.

Table 8. Clinical guidelines and guidance relevant to management of SHPT in UK

Organisation	Guideline / Guidance
NICE	NICE CG 182: Assessment and management of CKD in adults, 2014 [43]
	NICE CG 157: Chronic kidney disease (stage 4 or 5): management of hyperphosphatemia, 2013 [65]
	NICE TA 117: Cinacalcet for the treatment of SHPT in patients with end-stage renal disease on maintenance dialysis therapy, 2007 [15]
UK Renal Association	Clinical Practice Guideline: CKD-Mineral and Bone Disorders (CKD-MBD), 2015 [66]

European Renal Best Practice	Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement, 2010 [67]
Kidney Disease: Improving Global Outcomes (KDIGO)	KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), 2009 [11] (currently undergoing review)

3.2.2 Existing NICE guidance

NICE has issued several related guidelines and guidance on CKD, which collectively contribute to a complex pathway for the management of CKD. Elements relating to the management of SHPT within this CKD pathway are outlined below.

3.2.2.1 NICE Clinical Guideline 182: Assessment and management of CKD in adults

NICE issued clinical guideline 182 on the assessment and management of CKD in adults in 2014 [43]. This guideline does not provide specific recommendations for the treatment of SHPT in patients with CKD on haemodialysis, and states that detailed advice on the management of CKD–mineral and bone disorders (CKD-MBD, which is a term encompassing the multifactorial presentation of bone and mineral abnormalities, including abnormal biochemistry, vascular calcification, and altered bone structure in patients with CKD [47]) is beyond its scope. The following brief recommendations on the use of vitamin D in CKD are included:

- Do not routinely offer vitamin D supplementation to manage or prevent CKD-MDB
- Offer colecalciferol or ergocalciferol to treat vitamin D deficiency in people with CKD and vitamin D deficiency
- If vitamin D deficiency has been corrected and symptoms of CKD-MBD persist, offer alfacalcidol or calcitriol to people with a GFR <30ml/min/1.73m^2 (GFR category G4 or G5)
- Monitor serum calcium and phosphate concentrations in people receiving alfacalcidol or calcitriol supplements.

3.2.2.2 NICE Clinical Guideline 157: Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia

NICE issued clinical guideline 157 on the management of hyperphosphataemia in CKD stage 4 and 5 in 2013 [65]. This guideline notes that high serum phosphate levels can directly and indirectly increase PTH secretion, leading to the development of SHPT, which left untreated increases morbidity and mortality. For adult CKD patients on dialysis, this NICE guideline refers to the UK Renal Association guidelines on CKD-MBD, which recommend that serum phosphate levels be maintained at between 1.1 and 1.7 mmol/L [66].

The NICE guideline recommends restriction of dietary phosphate intake and use of a calcium-based phosphate binder. For adults with stage 5 CKD who are on dialysis and remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of calcium-based phosphate binder, the guideline recommends consideration of either combining with, or switching to, a non-calcium-based binder [65].

3.2.2.3 NICE Technology Appraisal TA 117: Cinacalcet for the treatment of SHPT in patients with end-stage renal disease on maintenance dialysis therapy

NICE conducted a technology appraisal of the daily oral calcimimetic cinacalcet in 2007 [15]. This noted that the aim of treatment in secondary hyperparathyroidism is to manage levels of phosphate, PTH and calcium. Conventional therapy at the time of the appraisal included dietary modification to reduce phosphate intake, the use of PB/VD, and modification of the dialysis regimen. It was noted that, in severe hyperparathyroidism, total or partial surgical removal of the parathyroid glands may be needed. No other calcimimetic agent was available.

Cinacalcet was not recommended by NICE for routine treatment of SHPT. Cinacalcet was recommended for restricted use in the treatment of refractory SHPT in patients with end-stage renal disease (including those with calciphylaxis) only in those [15]:

- who have 'very uncontrolled' plasma levels of intact PTH (defined as greater than 85 pmol/litre [800 pg/ml]) that are refractory to 'standard therapy', and a normal or high adjusted serum calcium level, and
- in whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits.

It should be noted that calcimimetic treatment was not well established as a part of 'standard therapy' at the time of the NICE appraisal of cinacalcet, and like vitamin D sterols and phosphate binders today, cinacalcet at that time was not well supported by clinical trial data demonstrating its effects on clinical outcomes.

3.2.3 Other relevant clinical guidelines

The NICE guidelines discussed above referred to the UK Renal Association guidelines on the management of CKD-MBD. In 2013 the UK Renal Association examined the internationally-respected 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for CKD-MBD [11] for their relevance to UK practice. The UK Renal Association adopted the KDIGO recommendations on diagnosis and treatment targets for abnormal biochemical parameters in this condition [66, 68]. European Renal Best Practice also endorsed the KDIGO clinical practice guidelines in 2010 [67]. Given their accepted relevance to the UK, the KDIGO clinical practice guidelines are discussed below.

3.2.3.1 KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD

The KDIGO clinical practice guideline was published in 2009 [11], two years after the NICE Technology Appraisal of cinacalcet [15]. The guideline indicates that the aim of treatment in SHPT is to maintain PTH within an acceptable target range to attenuate the important clinical consequences of SHPT and the accompanying calcium and phosphate disturbances [11]. The focus of SHPT treatment is therefore on the correction of biochemical abnormalities; these biochemical parameters are used to guide therapeutic decisions in practice.

PTH, calcium and phosphorous target levels

The guideline recommends maintaining intact PTH levels in the range of approximately 2 to 9 times the upper limit of normal for the assay, and also suggests that marked changes in intact PTH levels in either direction within this range should prompt an initiation or change in therapy to avoid progression to levels outside of this range. Calcium should be maintained within the normal range, and elevated phosphate levels should be lowered towards the normal range in

CKD patients on dialysis [11]. In general, therapeutic decisions should be based on trends, rather than a single laboratory value, and should take into account the entire available data set, rather than isolated variables [11].

It should be noted that evidence supporting these biochemical target recommendations is weak and of low quality [11].

Overview of treatment recommendations

The KDIGO guideline recommends limiting dietary phosphate intake and use of phosphate binders to treat hyperphosphatemia. To lower PTH in patients with elevated or rising levels, the guideline recommends use of vitamin D sterols or calcimimetic, or a combination of these. Parathyroidectomy is suggested in patients with severe SHPT who fail to respond to medical/pharmacological therapy [11].

3.3 *Current treatment options and clinical pathway for management of SHPT in the UK*

3.3.1 Phosphate binders and vitamin D sterols

Based on existing NICE guidance [15, 43, 65] and the KDIGO clinical practice guideline [11], it is clear that PB/VD are routinely recommended as part of medical management of SHPT. Treatment pattern data confirm that PB/VD are used by the large majority of dialysis patients in the UK (71% and 66% of patients, respectively, in 2011) [61], and the NICE Scope for this submission describes these agents as components of "established clinical care without calcimimetics" [22].

3.3.1.1 Strengths and limitations of phosphate binders and vitamin D sterols

PB/VD are routinely recommended treatments to address the biochemical abnormalities of SHPT and are well established in clinical practice. However, the mode of action of these agents may limit their effectiveness in practice, the evidence base supporting their use is limited, and there are significant challenges in adherence to these agents due to high pill burden and tolerability issues.

Limitations due to mode of action

Phosphate binders only affect dietary phosphate absorption, and the calcium content of phosphate binders recommended by NICE as first-line agents for treatment hyperphosphatemia [65] may contribute to hypercalcaemia and vascular calcification [13]. Vitamin D sterols reduce PTH levels via direct action on vitamin D receptors on parathyroid glands and by increasing gastrointestinal absorption of calcium and phosphate, but evidence from clinical trials and real-world use show an increased risk of hypercalcaemia and hyperphosphatemia with their use [12, 69, 70]. Therefore control of one biochemical parameter with use of these agents is often achieved at the expense of control of other parameters, which may exacerbate SHPT and its complications [13].

Limited evidence base

The 2015 UK Renal Association guideline notes that management of hyperphosphatemia remains difficult, as there are no RCTs assessing the benefits of phosphate lowering on patient survival. Recommendations are therefore driven by observational data [66]. Similarly, the NICE CKD guideline notes that, whilst replacing vitamin D in people with CKD is known to reduce hyperparathyroidism, and may provide potential benefits of increased bone mineral density and muscle strength, and reduced risks of falls, there is little data to suggest any benefit if vitamin D sterols on clinical outcomes, including all-cause mortality, CV mortality, CV events and fractures [43].

Pill burden, tolerability and adherence issues

Chronic kidney disease (CKD) patients on haemodialysis face one of the highest daily pill burdens of all chronic diseases [41], and adherence to prescribed oral medications is a widely recognised problem in these patients [18]. Recent international DOPPS data indicate that phosphate binders contribute to the high pill burden in ESRD patients; of 5,262 patients across 12 different countries about half were prescribed at least 6 phosphate binder pills per day and 13% were prescribed at least 12 phosphate binder pills per day. Around 45% of patients skipped phosphate binder doses in the previous month [14]. Gastrointestinal side effects are common with several phosphate binders [71].

3.3.2 Calcimimetic therapy

The 2007 NICE Technology Appraisal of cinacalcet recommended its use only in SHPT patients with 'very uncontrolled' PTH levels (>800pg/mL) that are refractory to 'standard therapy' [PB/VD regimens] and in who parathyroidectomy is contraindicated [15]. In contrast, the 2009 KDIGO clinical practice guideline recommends calcimimetic treatment as an option for the management of PTH levels without specific restriction [11].

The clinical landscape for SHPT has changed over the last 10 years since the NICE Technology Appraisal of cinacalcet was issued. For example, PTH target levels have been revised from the stringent 2003 K/DOQI guideline recommendations of 150-300pg/mL (around 2 to 4 times the upper limit of normal) [72], to the 2009 KDIGO guideline recommendation of 2 to 9 times the upper limit of normal, with marked changes in PTH levels in either direction within this range requiring initiation or change in therapy to avoid progression outside this range [11].

To understand the position of cinacalcet in the current treatment pathway, [redacted][15][redacted] Results of this survey therefore indicate that cinacalcet is routinely considered for use in clinical practice beyond the restricted recommendation of its 2007 NICE Technology Appraisal, and confirms it is used when PTH levels are high or remain uncontrolled with PB/VD. These findings are aligned with, and supported by the final NICE Scope for this submission, which requests comparison of etelcalcetide against cinacalcet for patients with refractory SHPT (without any further restriction) [22].

3.3.2.1 Strengths and limitations of calcimimetic therapy

The routine consideration for use of cinacalcet beyond the restricted recommendation for use in the 2007 NICE Technology Appraisal indicates the clinical utility of this calcimimetic in clinical practice. Cinacalcet is a highly effective in reducing PTH levels and serum calcium and phosphorus, and is supported by the strongest evidence base yet for any medical treatment of SHPT. However, as a daily oral therapy its effectiveness in real world settings is challenged by issues of poor adherence and discontinuation.

Strong evidence base

Compared with that for PB/VD, calcimimetic therapy has a strong evidence base supporting its use in SHPT. In its Technology Appraisal, cinacalcet was acknowledged by NICE to be effective in reducing levels of PTH and other biochemical markers, including serum calcium and phosphorus. Furthermore, NICE acknowledged the relationship between these biochemical parameters and adverse clinical events, and accepted the evidence review group's approach to modelling adverse clinical events based on PTH levels [15]. Since that appraisal, data from the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) RCT have become available, which alongside prior phase 3 RCT data, provides calcimimetic therapy with the strongest supporting evidence base yet for any medical treatment of SHPT.

EVOLVE outcomes trial

EVOLVE was specifically designed to assess clinical outcomes in SHPT patients treated with the daily oral calcimimetic cinacalcet [37, 56]. This large, double-blind, placebo-controlled trial randomised 3,883 patients with moderate to severe SHPT (median PTH 693 pg/mL) to receive treatment with cinacalcet plus PB/VD regimens, or placebo plus these therapies. The patient population was broadly representative of SHPT patients in clinical practice (see Section 3) and the treatment regimens employed were reflective of management in practice. Assessment of its internal validity and risk of bias is included in Appendix 4.

This was an event-driven trial in which patients were followed for up to 5 years. The primary endpoint was a composite of all-cause mortality and major CV events (myocardial infarction, hospitalisation for unstable angina, heart failure, or a peripheral vascular event) analysed on an intention-to-treat (ITT) basis. Secondary multivariable (covariate adjusted) analyses, to adjust for baseline characteristics, and companion lag-censored analyses, to adjust for any differences in time on treatment / persistence over the long follow-up period, were pre-specified in the protocol [37].

In the primary unadjusted ITT analysis, the addition of cinacalcet to PB/VD did not statistically significantly reduce the risk of the composite primary endpoint of all-cause mortality and major cardiovascular events (hazard ratio: 0.93; 95% CI 0.85 to 1.02; p=0.11). However, there was a chance imbalance in age between the cinacalcet and placebo arms, a higher incidence of treatment discontinuation than was expected in both arms, and a high proportion (20%) of placebo recipients received commercially available cinacalcet before the occurrence of a primary event. The pre-specified secondary and companion analyses that specifically adjusted for these types of confounding factors consistently favoured the addition of cinacalcet compared with PB/VD therapies alone:

- Covariate adjusted ITT analyses, which adjusted for imbalances in baseline characteristics, showed the addition of cinacalcet to PB/VD significantly reduced the risk of the composite primary endpoint of all-cause mortality and major cardiovascular events (hazard ratio: 0.88; 95% CI, 0.79 to 0.97; nominal p = 0.008) [37].

- Lag-censored analyses, which adjusted for differences in time on treatment and account for the high levels of cinacalcet use in the placebo recipients, showed addition of cinacalcet to PB/VD therapies significantly reduced the risk of the composite primary endpoint of all-cause mortality and major cardiovascular events (hazard ratio 0.85 (95% CI, 0.76 to 0.95; nominal p=0.003) and all-cause mortality (hazard ratio, 0.83 (95% CI, 0.73 to 0.96; nominal p=0.009) [37].

In summary, when adjusted for the confounding factors of imbalances in age, high levels of treatment discontinuation, and commercial cinacalcet use, the EVOLVE trial demonstrated that addition of calcimimetic therapy to PB/VD significantly reduces the risk of adverse clinical events compared with PB/VD alone. These results were consistent across multiple adjusted analyses within the EVOLVE trial, were consistent with retrospective combined analyses of previous cinacalcet RCTs that also observed significant improvements in clinical outcomes with addition of cinacalcet to PB/VD [73], and are biologically plausible given the known pathophysiology of SHPT and the associated adverse clinical events. Of note, the European Medicines Agency agreed the inclusion of the results of the EVOLVE trial, including the co-variate adjusted ITT analyses of the primary endpoint, in the Mimpara® (cinacalcet) SmPC [40], and the UK Renal Association clinical practice guideline notes the co-variate adjusted analyses of the EVOLVE trial significantly favoured cinacalcet, and concluded it is '…*clear from the EVOLVE trial that it is an extremely effective treatment to control hyperparathyroidism…*' [66].

Adherence and discontinuation issues

Cinacalcet is a daily oral calcimimetic therapy [40]. It is a potent inhibitor of PTH and is recognised in UK clinical guidelines as highly effective in the treatment of SHPT [66]. However, its effectiveness in clinical practice is limited by poor adherence and high discontinuation rates. [redacted] Recent real world data from Europe indicate rates of discontinuation 1 year after initiation of cinacalcet are as high as 59% in Italy and 46% in France (when defined by a prescription gap of 30 days) [35, 36]. The lag censored analyses of the EVOLVE trial, which account for time on treatment, confirm that cinacalcet therapy is highly effective when taken [37], and observational data indicate that patients who persist with cinacalcet treatment have improved survival compared with those who discontinue [42]. Therefore, improved adherence and persistence with calcimimetic therapy in practice would be expected to deliver improved effectiveness.

3.3.3 Parathyroidectomy

The KDIGO clinical practice guidelines suggest parathyroidectomy as a treatment modality in patients with severe SHPT who fail to respond to medical/pharmacological therapy [11]. However, parathyroidectomy is an invasive, irreversible surgical procedure that is associated with distinct risks of sustained inappropriately low PTH levels, leading to more complex disease management and associated high costs [20, 21]. Therefore, as suggested in clinical guidelines [11], parathyroidectomy should be considered a treatment of last resort when all medical therapies have been exhausted.

Whilst noting that parathyroidectomy is a treatment option for some patients with SHPT that is refractory to PB/VD therapy, NICE acknowledged that etelcalcetide would not displace surgical treatment [24], and therefore parathyroidectomy is not considered to be an appropriate comparator in the NICE Scope for this appraisal [22].

3.4 *Position of etelcalcetide in the clinical pathway*

Existing treatment options for patients with SHPT are associated with a number of limitations, as discussed above. There are clear unmet needs for a more effective alternative treatment option to cinacalcet, that is convenient and does not contribute to the high pill burden for these patients, and that facilitates greater adherence and persistence (continued treatment) to ensure patients with SHPT can achieve the best possible outcomes from medical therapy.

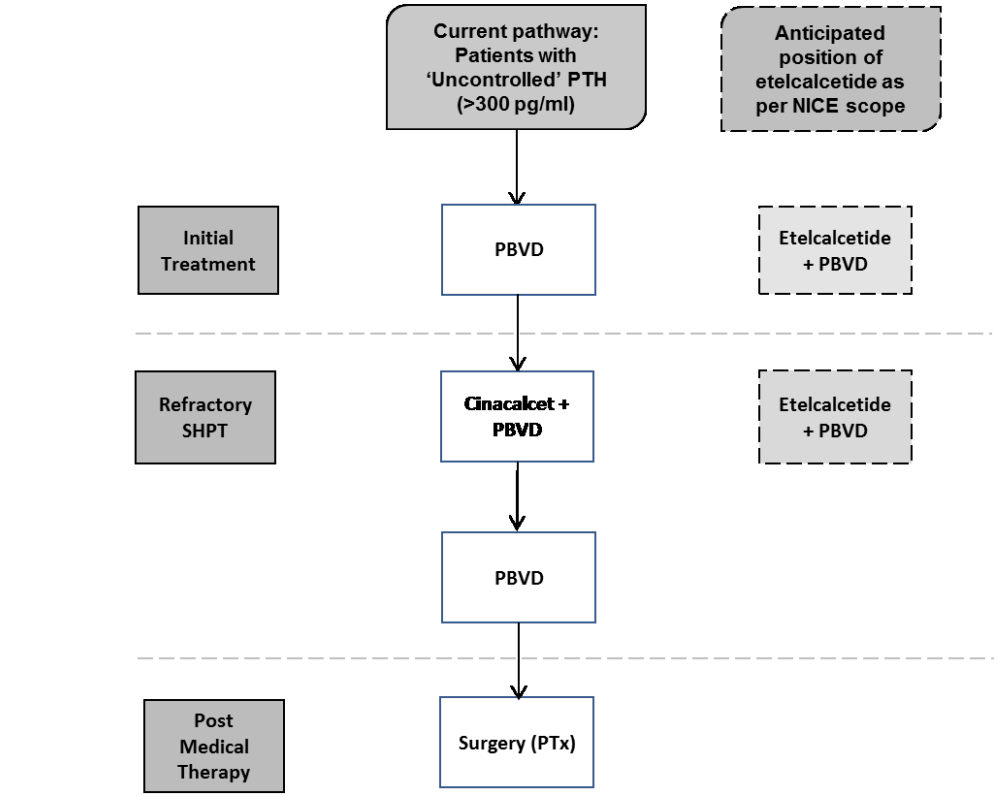
Etelcalcetide is an innovative IV calcimimetic that can address these unmet needs:

- Etelcalcetide modulates SHPT by binding to and activating the calcium-sensing receptors (CaSR) in the parathyroid glands, at a site that is distinct from the sites activated by calcium and the daily oral calcimimetic cinacalcet, to reduce secretion of PTH. The reductions in PTH are accompanied by reductions in phosphorous and calcium.
- Etelcalcetide has demonstrated superior, clinically meaningful SHPT control over placebo and cinacalcet when all are added to PB/VD regimens. Results are consistent in the broad population of patients with SHPT meeting its licensed indication, and in distinct subgroups defined by patient demographics, severity of SHPT and prior use of cinacalcet (see section 4.7). Etelcalcetide is also well tolerated, with an adverse event profile similar to cinacalcet. (see section 4.12).
- Etelcalcetide is administered intravenously three times per week at the end of routine haemodialysis sessions, which provides healthcare professionals with complete control over its administration, reduces pill burden and improves patient convenience, and may facilitate improved adherence and persistence compared with daily oral therapy.

With a positive CHMP opinion for the '*treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy'* [27], etelcalcetide will be indicated across the broad population of patients with SHPT, irrespective of disease severity and prior or concomitant therapy. In practice, it is anticipated that etelcalcetide will be administered in addition to PB/VD, as per its use in phase 3 clinical trials.

This submission reflects the positioning of etelcalcetide across this broad SHPT patient population, for which treatment with PB/VD is the established comparator, and the distinct population of patients with refractory SHPT, for which cinacalcet is the relevant comparator, in line with the NICE scope [22] (Figure 2).

Figure 2: Current SHPT pathway and anticipated positioning of etelcalcetide



PBVD, Phosphate binders + Vitamin D;

4 Clinical effectiveness

Summary

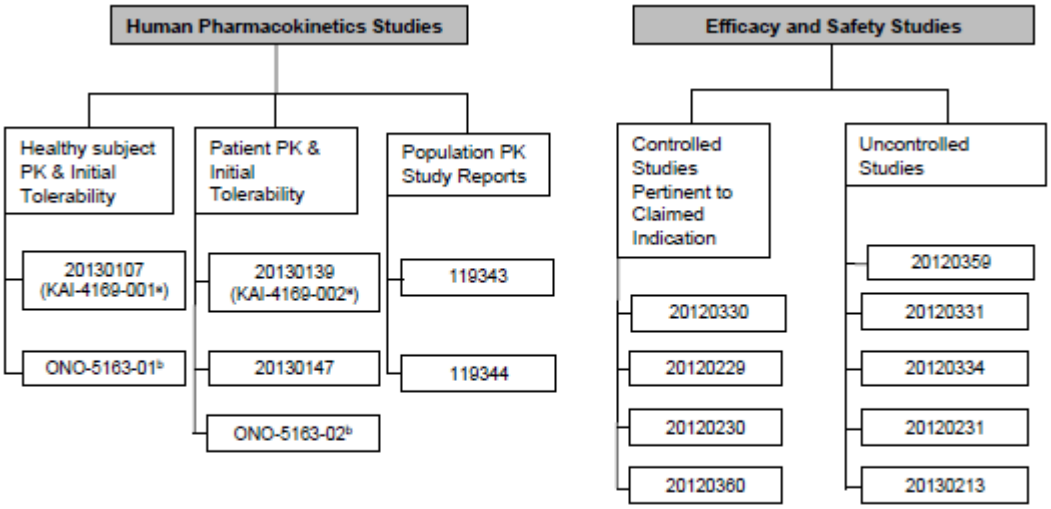
- Key efficacy and safety data for etelcalcetide are available from three robust, double-blind, multinational, 26-week RCTs. These include two near-identical placebo-controlled RCTs that enrolled patients with baseline PTH >400pg/mL and one RCT that directly compared etelcalcetide against cinacalcet in patients with baseline PTH >500pg/mL. In all three trials, etelcalcetide and the comparators were added to background therapies including PB/VD, in line with their expected use in practice.
- In placebo-controlled trials, etelcalcetide significantly reduced PTH levels relative to placebo as measured by achievement of a clinically relevant >30% reduction in mean PTH from baseline, mean PTH ≤ 300 pg/mL, and percent change in mean PTH from baseline during the efficacy assessment phase (EAP, weeks 20-27). Significant percent reductions from baseline in mean cCa, P and cCa x P were also observed for etelcalcetide compared with placebo during the EAP
- In the active-controlled trial, following demonstration of non-inferiority, etelcalcetide demonstrated superiority over cinacalcet for both the achievement of a >30% and >50% reduction in mean PTH from baseline during the EAP (weeks 20-27). This superior efficacy was achieved despite greater persistence to cinacalcet in the trial than is observed in clinical practice.
- Results were consistent across pre-defined subgroups, including patient demographics, dialysis vintage, severity of SHPT, and prior use of cinacalcet.
- Etelcalcetide was well tolerated, with an adverse event profile consistent with the mechanism of action of calcimimetics. The patient incidence of decreased blood calcium and symptomatic hypocalcaemia was higher among patients who received etelcalcetide compared with placebo or cinacalcet; however, these events were mild or moderate in severity, are readily manageable, and rarely led to permanent discontinuation.
- The trials had high internal and external validity, and results are at low risk of bias. Enrolled patients were broadly representative of dialysis patients with SHPT anticipated to use etelcalcetide in clinical practice, including patients with prior cinacalcet use suggesting a history of refractory SHPT. The trials assessed biochemical endpoints that are relevant to the management of SHPT in clinical practice and were considered clinically meaningful by the CHMP. The link between these biochemical endpoints and clinical outcomes is well established, as accepted by NICE in its 2007 appraisal of cinacalcet.
- Extension studies, providing up to 18 months of follow-up data for patients enrolled in RCTs, show that the efficacy and safety of etelcalcetide are maintained with long-term treatment.
- In summary, these robust data indicate that etelcalcetide provides superior SHPT control compared with placebo and cinacalcet when added to phosphate binder and/or vitamin D sterols in the broad range of patients with SHPT meeting its licensed indication, including those who are refractory to treatment with phosphate binder and vitamin D regimens alone.

4.1 *Identification and selection of relevant studies*

4.1.1 Studies supporting the etelcalcetide marketing authorisation application

The comprehensive marketing application comprised 14 clinical studies conducted between 2010 and 2015 to support the use of etelcalcetide for the treatment of SHPT in patients with CKD receiving haemodialysis. Of these studies, two were conducted in healthy volunteers, and 12 were conducted in patients with SHPT receiving maintenance haemodialysis. Four RCTs relevant to the proposed licensed indication were included: three 26-week phase 3 RCTs (studies 20120229, 20120230 and 20120360), and one small, 4-week, phase 2, ascending dose RCT (study 20120330) (Figure 3). Of these, the three larger, and longer phase 3 RCTs are considered the most relevant to address the decision problem in this submission, and to confirm this the results or a systematic literature review have been used to identify any and all relevant etelcalcetide RCTs (see below).

Figure 3: Etelcalcetide clinical development programme supporting marketing authorisation



PK = pharmacokinetics
[a] These studies were conducted by KAI Pharmaceuticals before its acquisition by Amgen.
[b] These studies were conducted in Japan by an Amgen business partner.

4.1.2 Systematic literature review of etelcalcetide trial data

A systematic literature review (SLR) was conducted to identify [redacted] any and all etelcalcetide trials relevant to the decision problem, as detailed below.

4.1.3 Search strategy

The search strategy aimed to identify all relevant trials of etelcalcetide [redacted] supplemented with searches of unpublished trial data from Amgen files and information from grey literature sources, including conference abstracts and clinical trial databases.

The following databases were searched for relevant clinical studies (see Section 4.1.4) from inception to January 2015, with an update conducted to July 2016:

- Medline (OvidSP): 1946 to 2016/07/wk1
- Medline In-Process Citations (OvidSP): up to 2016/07/18
- Medline Daily Update (OvidSP): up to 2016/07/18
- National Library of Medicine (NLM) PubMed (Internet) (This is the companion search outlined in stage one): up to 2016/07/20
- Embase (OvidSP): 1974-2016/07/18
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Cochrane Library 2016/June/Iss6/
- NIHR Health Technology Assessment Programme (Internet): http://www.hta.ac.uk/: up to 2016/07/19
- PROSPERO (International Prospective Register of Systematic Reviews): http://www.crd.york.ac.uk/prospero/: up to 2016/07/19
- Literature in the Health Sciences in Latin America and the Caribbean (LILACS) (Internet):http://lilacs.bvsalud.org/en/: 1982-2016/07/19

Grey literature was identified from searches of the resources listed below:

- European Medicines Agency (EMA) (Internet): http://www.ema.europa.eu/ema/: up to 2016/07/19
- US Food & Drug Administration (FDA) (Internet): http://www.fda.gov/: up to 2016/07/19

Supplementary searches were undertaken on the following trials registers to identify completed and ongoing trials, from inception to mid-July 2016:

- NIH Clinicaltrials.gov (Internet): http://www.clinicaltrials.gov/: up to 2016/07/20
- ISRCTN registry (Internet): http://www.isrctn.com/: up to 2016/07/20
- PharmNet.Bund (Internet): http://pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm: up to 2016/07/20
- EU Clinical Trials Register (EUCTR) (Internet): https://www.clinicaltrialsregister.eu/ctr-search/search: up to 2016/07/20
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet): http://www.who.int/ictrp/en/: up to 2016/07/26
- Australian New Zealand Clinical Trials Registry (Internet): http://www.anzctr.org.au/: up to 2016/07/20

Appendix 3 details the search strings that were developed specifically for each database. Key words were adapted according to the configuration of each database and, where appropriate, fully referenced study design filters for RCTs were used. Only studies conducted in humans were sought. Searches were not limited by date or language.

4.1.4 Study selection

The criteria used for study selection in the broad SLR are detailed in Table 9. These criteria were chosen to ensure inclusion of the most relevant data for SHPT treatments in terms of patients, interventions, comparators, outcomes and study designs, and are broadly aligned with the NICE Scope for this appraisal [22]. These criteria were further refined to identify only

RCTs of etelcalcetide, ensuring the most relevant data for addressing the decision problem defined by the Scope were identified. Studies not meeting these criteria were excluded.

4.1.5 Systematic literature review results

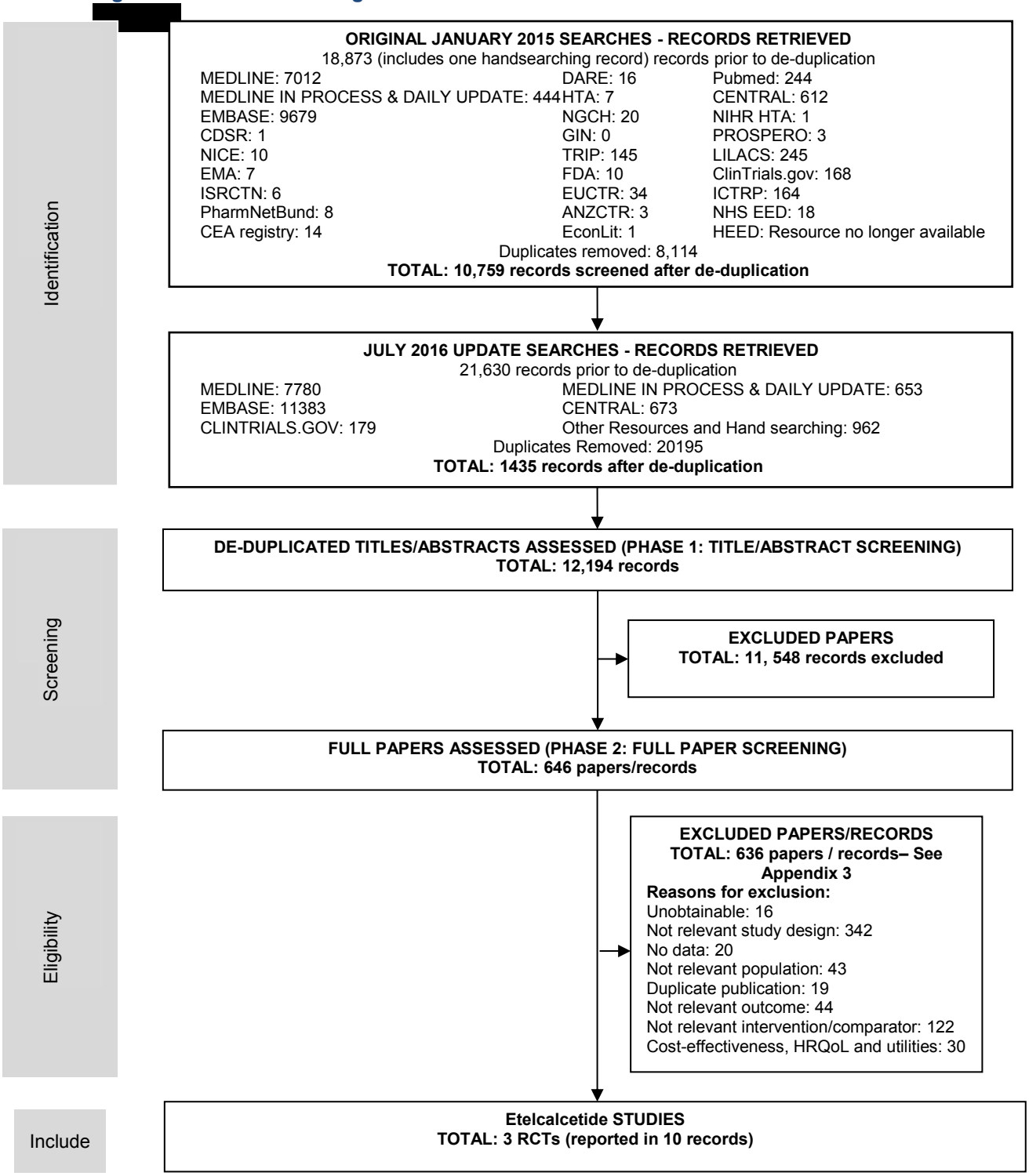
Figure 4 presents the PRISMA flow diagram for the SLR. After de-duplication, 12,194 records were retrieved and their titles and abstracts screened by two reviewers independently for relevance according to the inclusion criteria for the review (Phase 1 screen). Any discrepancies were resolved through consensus or consultation with a third reviewer. From these records, a total of 646 were identified for full paper/report screening (Phase 2 screening). The full papers/reports were screened in detail by two independent reviewers, to determine whether they fulfilled the review inclusion criteria. When limited to trials including etelcalcetide, this yielded 10 reports providing details of three randomised controlled trials of etelcalcetide. Details of the 636 papers/reports that were excluded are included in Appendix 3.

The three etelcalcetide trials identified in the SLR provide the key efficacy and safety data for etelcalcetide in this submission, and were included as registration studies in the marketing authorisation application to the European Medicines Agency. Supporting non-randomised trial data are included in section 4.11.

Table 9: SLR inclusion criteria

Criteria	Inclusion criteria	Justification and relevance to the decision problem
Population	Adult (≥ 18 years) CKD patients with SHPT undergoing haemodialysis.	Etelcalcetide is anticipated to be licensed specifically in this patient population [23]. NICE will appraise etelcalcetide within its licensed indication [ref Scope]
Intervention and Comparators	• Etelcalcetide (AMG 416; formerly known as velcalcetide) administered in line with its anticipated licensed dose [23]. • Cinacalcet • Parathyroidectomy • PB/VD (which may include one or more of the following - calcitriol, other vitamin D analogues, and/or phosphate binders) • Placebo as a comparator Patients could also receive any necessary background therapy (PB/VD) in the form of vitamin D, vitamin D analogues, and/or phosphate binders as necessary, provided that the same background therapy was available for both the intervention and any comparator groups.	The broad SLR permits identification of relevant etelcalcetide trials. Identifies trials of etelcalcetide used in accordance with the anticipated licensed dose [23].
Outcomes	At least one of the following outcomes: • Clinical outcomes: e.g. Overall survival (OS); Incidence of fractures; Incidence of fatal or non-fatal CV events (composite and individual outcomes) (e.g. CV death, CHD, MI, ischemic stroke, TIA, hospitalisation for unstable angina, hospitalisation for worsening heart failure, symptomatic PAD, CHD and coronary revascularisation); Incidence of PTx • Biochemical outcomes: ○ Proportion of patients with a predefined reduction from baseline in PTH, serum calcium, serum phosphorus (P) • Safety outcomes: e.g. Number and proportion of patients experiencing any AE (all events/treatment related/treatment emergent), serious AEs (all events/treatment related/treatment emergent), specific AEs associated with SHPT treatments • Patient-reported outcomes (absolute values or change from baseline): e.g. Health related quality of life (HRQoL) assessed using any reported tool	Reflect relevant clinical, biochemical and patient-oriented outcomes that may usefully address the decision problem.
Study design	Randomised controlled trials (RCTs) of at least 12 weeks treatment duration.	RCTs generally provide the most robust data for evaluating clinical efficacy. Requirement for at least 12 weeks of treatment reflects the fact etelcalcetide is a long term treatment for SHPT (and is aligned with the criteria used by the ERG to identify cinacalcet trial data for NICE TA117 [75])

Figure 4: PRISMA flow diagram. Identification and selection of etelcalcetide trials



4.2 *List of relevant randomised controlled trials*

The SLR identified the three phase 3 etelcalcetide RCTs included in the marketing authorisation application to the European Medicines Agency, confirming that these provide the relevant RCT data to address the decision problem outlined in the NICE scope [22]. These are summarised in Table 10 and include:

- Two phase 3 placebo-controlled trials (studies 20120229 and 20120230), whose near-identical design allowed an integrated analysis to be conducted. These studies evaluated addition of etelcalcetide to treatment with PB/VD against addition of placebo to treatment with PB/VD, in the broad licensed patient population for etelcalcetide.

- A phase 3 active-controlled trial (study 20120360), which evaluated etelcalcetide against cinacalcet, both in addition to treatment with PB/VD, in the broad licensed patient population for etelcalcetide. This trial was powered to detect non-inferiority for the primary endpoint, followed by superiority for key secondary endpoints.

None had been fully published as manuscripts at the time of writing, and all details are derived from the clinical study reports and summary regulatory documentation, and conference presentations.

The marketing authorisation application also included a small, 4-week, phase 2, placebo-controlled, ascending-dose trial (study 20120330), which is less relevant to the decision problem compared with the three longer and larger phase 3 trials and is not further discussed. Details of relevant non-comparative studies are discussed in section 4.11.

Table 10: Relevant RCTs of etelcalcetide

Trial ID	Population	Intervention	Comparator	Primary reference
20120229 & 20120230	Adults ≥ 18 years of age with CKD receiving haemodialysis (TIW) for ≥ 3 months; stable dialysate calcium concentration (≥ 2.25 mEq/L) and screening predialysis PTH of > 400 pg/mL and cCa ≥ 8.3 mg/dL. Participants receiving vitamin D sterols, phosphate binders, or calcium supplements must have been on stable doses.	IV **etelcalcetide** administered at the end of each haemodialysis session (TIW). Starting dose of 5mg. Dose could be increased at 4-wk intervals by 2.5mg or 5mg on the basis of the predialysis PTH and cCa concentrations obtained in the prior week. Minimum dose was 2.5mg and maximum dose was 15mg. All received background thearpy which could have included calcium supplements, vitamin D sterols, nutritional vitamin D, and phosphate binders, as prescribed by the individual investigator.	IV **Placebo** administered at the end of each haemodialysis session (TIW). Presented in identical containers and stored/packaged in the same manner as etelcalcetide. All received background therapy as per the etelcalcetide arm	20120229 CSR [28] 20120230 CSR [29]
20120360	Adults ≥ 18 years of age with CKD receiving haemodialysis (TIW) for ≥ 3 months; stable dialysate calcium concentration (≥ 2.5 mEq/L) and screening predialysis PTH of > 500 pg/mL and cCa ≥ 8.3 mg/dL.	IV **etelcalcetide** administered at the end of each haemodialysis session (TIW) (+ oral cinacalcet placebo provided in same manner as cinacalcet in cinacalcet arm.) Etelcalcetide starting dose 5mg. Dose could be increased at 4-wk intervals by 2.5mg or 5mg on basis of the predialysis PTH and cCa concentrations obtained in the prior week. Minimum dose was 2.5mg and maximum dose was 15mg. All received background therapy which could include calcium supplements, vitamin D sterols, nutritional vitamin D, and phosphate binders, as prescribed by the individual investigator.	Oral **Cinacalcet** (+ IV etelcalcetide placebo provided in same manner as etelcalcetide in etelcalcetide arm) Cinacalcet 30mg daily oral starting dose. Titrated every 4wks (up to 180mg max). All received background therapy as per the etelcalcetide arm	20120360 CSR [30]
cCa, corrected serum calcium; CKD, chronic kidney disease; IV, intravenous; PTH parathyroid hormone; TIW, three times per week				

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Placebo-controlled trials (Study 20120229 and 20120230): design and methodology

The two phase 3, multinational, randomised, double-blind, placebo-controlled trials were conducted in parallel and aimed to demonstrate superiority of etelcalcetide over placebo in terms of reducing PTH level by > 30% from baseline [28, 29] [76]. Adult chronic kidney disease patients with PTH levels >400pg/mL were randomised 1:1 to 26 weeks of treatment with etelcalcetide 5mg or placebo three times per week (TIW) at the end of haemodialysis sessions, on a background of PB/VD where necessary. Treatment allocation was concealed, and randomisation was stratified by mean screening PTH (< 600, 600 to 1000, > 1000 pg/mL), recent cinacalcet use (yes or no within 8 weeks prior to randomization), and region (North America, non-North America) to ensure balance in disease severity, previous calcimimetic exposure, and regional practice patterns between treatment groups. The dose was titrated in 2.5 or 5 mg increments every 4 weeks to a maximum dose of 15 mg three times per week, to target PTH levels to <300 pg/mL. Both groups could receive PB/VD (active vitamin D, phosphate binders, and calcium supplements), and if receiving these at baseline had to be on stable doses. Cinacalcet was not permitted during the 4 weeks prior to screening or on study.

The primary endpoint – proportion of patients with >30% reduction from baseline in PTH levels – was assessed during the Efficacy Assessment Phase (EAP, weeks 20-27). Secondary efficacy endpoints were only tested for significance if the primary endpoint was significant ($p<0.05$). Efficacy analysis was based on the Full Analysis Set , which included all randomized patients (i.e., intention to treat analysis) and those patients with data missing during the EAP were considered to have not achieved the endpoint (i.e., non-responder imputation).

The two placebo-controlled studies were identical in design except that pre- and post-dialysis assessments of electrocardiograms (ECGs), laboratory data and pharmacokinetic data were performed in Study 20120229, whereas only pre-dialysis assessments were performed in Study 20120230 [28, 29]. This allowed an integrated analysis of both efficacy and safety. A schematic of the design of the RCTs is provided in Figure 5 (for the placebo-controlled studies the two arms were etelcalcetide and placebo IV TIW) and further details of the trial designs and methodology are provided in Table 11.

4.3.2 Active-controlled study comparing etelcalcetide with cinacalcet (Study 20120360): design and methodology

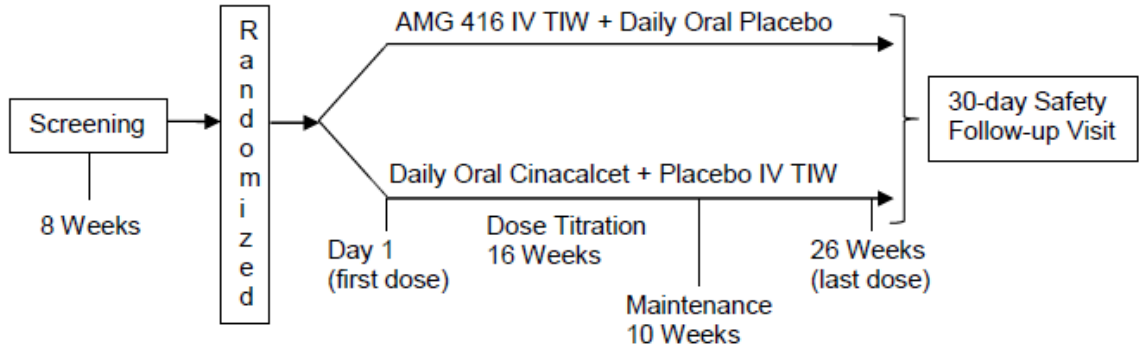
The active-controlled, multinational, phase 3, randomised, double-blind, double-dummy trial (20120360) was conducted to compare the efficacy and safety of etelcalcetide against cinacalcet, both on a background of PB/VD where necessary [30] [77]. Adult chronic kidney disease patients with PTH levels >500pg/mL were randomised 1:1 to 26 weeks of treatment with etelcalcetide 5mg TIW during haemodialysis sessions (plus daily oral placebo), or cinacalcet tablets 30mg once daily (plus IV placebo TIW at the end of haemodialysis sessions). Doses of study drug were titrated to target PTH levels $\leq$300 pg/mL. Treatment allocation was concealed, and randomisation was stratified by region (North America, non-North America) and mean screening PTH (< 900, $\geq$ 900pg/mL) to ensure balance in regional practice patterns and disease severity between treatment groups. The PTH strata differed from the placebo-controlled studies due to the higher PTH eligibility criterion in this study.

The primary objective of this study was to demonstrate that treatment with etelcalcetide was non-inferior to treatment with cinacalcet for lowering PTH levels by > 30% from baseline during the EAP (weeks 20-27). Further, if non-inferiority was demonstrated, the study could proceed to sequentially test whether or not treatment with etelcalcetide was superior to treatment with cinacalcet as measured by the three key secondary endpoints:

1. reduction of PTH by > 50% from baseline during the EAP
2. reduction of PTH by > 30% from baseline during the EAP
3. mean number of days of nausea and vomiting per week during the first 8 weeks

Efficacy analysis was based on the Full Analysis Set which included all randomized patients [30]. A schematic of the trial is provided in Figure 5 and further detail of the trial design and methodology are provided in Table 11.

Figure 5: Schematic of general design of etelcalcetide RCTs (study 20120360 shown)



IV = intravenous; TIW = 3 times a week

AMG 416 = Parsabiv™

Table 11: Comparative summary of the etelcalcetide phase 3 trial designs and methodologies

Features of design and methodology	Placebo-controlled studies 20120229 [28] & 20120230 [29]	Active-controlled study 20120360 [30]
Settings and locations	**20120229:** 111 renal centres in the United States (US), Canada, Europe, Israel, Russian Federation, and Australia. **20120230:** 97 renal centres in the United States (US), Canada, Europe, Israel, Russian Federation, and Australia.	164 renal centres in the United States (US), Canada, Europe, Russian Federation, and New Zealand.
Trial design	26-week, phase 3, multicentre, randomized, double-blind, placebo-controlled study. Comprised a screening period of up to 8 weeks to determine eligibility, followed randomisation of eligible participants and entry into a 26-week treatment period (16 weeks dose titration and 10 weeks maintenance) and finally a 30-day follow-up period.	26-week, phase 3, multicentre, randomized, double-blind, double-dummy, active-controlled study. Comprised a screening period of up to 8 weeks to determine eligibility, followed randomisation of eligible participants and entry into a 26-week treatment period (16 weeks dose titration and 10 weeks maintenance) and finally a 30-day follow-up period.
Eligibility criteria for participants	**Inclusion:** Adults ≥ 18 years of age receiving haemodialysis (TIW) for ≥ 3 months; and had stable dialysate calcium concentration (≥ 2.25 mEq/L) and screening predialysis PTH of > 400 pg/mL and cCa ≥ 8.3 mg/dL. Participants who were receiving vitamin D sterols, phosphate binders, or calcium supplements must have been on stable doses. **Exclusion:** Received cinacalcet within 4 weeks of screening; had a parathyroidectomy within 3 months of dosing; were anticipated to undergo a parathyroidectomy or kidney transplant during the treatment period; history of certain cardiovascular diseases or cardiac abnormalities; history of seizure or receiving treatment for seizure disorder; pregnancy.	**Inclusion:** Adults ≥ 18 years of age receiving haemodialysis (TIW) for ≥ 3 months; stable dialysate calcium concentration (≥ 2.5 mEq/L) and screening predialysis PTH of > 500 pg/mL and cCa ≥8.3mg/dL (within 2 weeks of randomisation and obtained by one central laboratory screening). Participants who were receiving vitamin D sterols, the vitamin D dose must have had no more than a maximum dose change of 50% within the 4 weeks before screening. Participants receiving calcium supplements or phosphate binders must have had no more than a maximum dose change of 50% within 2 weeks before screening. Phosphate binder doses must have been expected to remain stable for the duration of the study and calcium doses stable through randomisation, except as noted in the protocol. **Exclusion:** Participants who have received cinacalcet in the 3 months before screening; had a parathyroidectomy within 3 months of dosing; were anticipated to undergo a parathyroidectomy or kidney transplant during the treatment period; history of certain cardiovascular diseases or cardiac abnormalities; history of seizure or receiving treatment for seizure disorder; pregnancy.
Allocation and Randomisation	Allocation concealed. Computer randomisation using a 1:1 ratio, stratified by mean screening PTH (< 600 pg/mL, 600 to ≤ 1000 pg/mL, and > 1000 pg/mL) obtained within 2 weeks before randomisation, prior cinacalcet use (within 8 weeks before randomization), and region (North America or non-North	Allocation concealed. Computer randomisation using a 1:1 ratio, stratified by serum PTH concentration (< 900 or ≥ 900 pg/mL) and region (North America or non-North America).

	America). Enrolment of subjects with mean screening PTH > 1000 pg/mL was limited to approximately 20% of subjects.	
Trial drugs	**20120229:** **Etelcalcetide (n=254):** Administered intravenously at the end of each haemodialysis session (TIW) for 26 weeks. Starting dose of 5 mg. Dose could be increased at 4-week intervals by 2.5 mg or 5 mg on the basis of the predialysis PTH and cCa concentrations obtained in the prior week. Dose range 2.5 mg to 15 mg. **Placebo (n=254):** Administered intravenously at the end of each haemodialysis session (TIW) for 26 weeks. Presented in identical containers and stored/packaged in the same manner as etelcalcetide. **20120230:** **Etelcalcetide (n=255):** Administered as for 20120229 **Placebo (n=260):** Administered as for 20120229 **Background therapy (both groups and both trials):** All received therapy which could have included calcium supplements, vitamin D sterols, nutritional vitamin D, and phosphate binders, as prescribed by the individual investigator.	**Etelcalcetide (+ oral cinacalcet placebo) (n=340):** Administered intravenously at the end of each haemodialysis session (TIW) for 26 weeks. Starting dose of 5 mg. Dose could be increased at 4-week intervals by 2.5 mg or 5 mg on the basis of the predialysis PTH and cCa concentrations obtained in the prior week. Dose range 2.5 mg to 15 mg. Placebo for oral cinacalcet provided in same manner as in cinacalcet arm. **Cinacalcet (+ IV Etelcalcetide placebo) (n=343):** 30mg daily oral starting dose. Titrated every 4wks (up to 180mg max). Placebo for IV etelcalcetide provided in same manner as in etelcalcetide arm. **Background therapy (both groups):** All received therapy as prescribed by the individual investigator, with calcium supplements, phosphate binders, and nutritional vitamin D supplements. If treatment with calcitriol or vitamin D analogues was ongoing when subjects were enrolled in the study, the doses of these agents were to remain constant for the duration of study; however, treatment with vitamin D was initiated, interrupted, or adjusted for reasons of safety
Treatment target	Predialysis PTH ≤ 300 pg/mL	As for 20120229 and 20120230
Primary outcomes	Proportion of participants with > 30% decrease from baseline in mean PTH during the EAP (defined as weeks 20 to 27, inclusive).	Test of non-inferiority for proportion of participants with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP.
Secondary/ tertiary / other outcomes	**Secondary outcomes:** ○ Proportion of subjects with predialysis PTH ≤ 300 pg/mL during the EAP (defined as weeks 20 to 27, inclusive). ○ % change from baseline in predialysis PTH, cCa, cCa x P and P during the EAP (defined as weeks 20 to 27, inclusive). **Tertiary and other outcomes:** ○ Nature, frequency, severity, and relationship to treatment of all adverse events reported throughout the study. ○ Vital signs and changes in ECG and laboratory parameters, including clinical chemistry. ○ Evaluation of antibody formation to etelcalcetide.	**Secondary outcomes:** Sequential test of superiority for: 1. Proportion of participants with > 50% reduction from baseline in mean predialysis serum PTH during the EAP. 2. Proportion of participants with > 30% reduction from baseline in mean predialysis serum PTH during the EAP 3. Mean number of days of vomiting or nausea per week in the first 8 weeks. ○ % change from baseline in mean predialysis serum cCa during the EAP.

	○ Pharmacokinetic and biomarker analyses (i.e., FGF-23, BSAP, CTX). ○ Plasma AMG 416 concentration at weeks 4, 5, 12, 13, 20, and 26, and at follow-up ○ Absolute change in log FGF-23 levels, BSAP levels, and CTX levels from baseline to the week 12 and week 27 visits	○ % achieving mean predialysis serum phosphorus ≤ 4.5 mg/dL during the EAP. ○ Mean severity of nausea in the first 8 weeks. ○ Mean number of episodes of vomiting per week in the first 8 weeks. **Tertiary and other outcomes:** ○ Nature, frequency, severity, and relationship to treatment of all adverse events reported throughout the study. ○ Incidence of cCa < 8.3 mg/dL, cCa < 8.0 mg/dL, cCa < 7.5 mg/dL, symptomatic hypocalcaemia and serum P > 5.5 mg/dL at any time during the study ○ % change from baseline in mean predialysis phosphorus during the EAP. ○ % achieving mean predialysis serum PTH ≤ 300 pg/mL during the EAP. ○ Change in serum BSAP, CTX, and FGF-23 from baseline to week 27. ○ Mean number of episodes of vomiting per week and mean severity of nausea in the first 16 or 26 weeks. ○ Health-related quality of life assessed by KDQOL-36
Pre-planned subgroups	○ Screening PTH category (< 600 pg/mL, ≥ 600 to ≤ 1000 pg/mL, and > 1000 pg/mL); ○ Prior cinacalcet use (within 8 weeks before randomization (Yes, No); ○ Region (North America or non-North America); ○ Dialysate calcium (< 2.5 or ≥ 2.5 mEq/L); ○ Race (Black, White/Other); ○ Dialysis vintage (0 to ≤ 1 year, 1 to ≤ 5 years, > 5 years); ○ Vitamin D sterol use (Yes, No); ○ Calcium containing phosphate binder or calcium supplement use (Yes, No)	○ Screening PTH concentration (< 900 pg/mL, ≥ 900 pg/mL); ○ Region (North America, non-North America); ○ Race group (Black, White/other); ○ Dialysis vintage (> 0 to ≤ 1 year, > 1 to ≤ 5 years, > 5 years); ○ Baseline vitamin D sterol use (Yes, No); ○ Baseline calcium-containing phosphate binder or calcium supplement use (Yes, No); ○ Previous cinacalcet use (Yes, No); ○ Dialysate calcium (< 3.0 mEq/L, ≥ 3.0 mEq/L); ○ Sex (Men, women); ○ Age (< 65 years, ≥ 65 years).
cCa, corrected serum calcium; CKD, chronic kidney disease; EAP, Efficacy assessment phase; IV, intravenous; P, phosphorous; PTH parathyroid hormone; TIW, three times per week		

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Placebo-controlled trials (Study 20120229 and 20120230): statistical analysis and study groups

A planned sample size of 500 for each of the placebo-controlled trials was chosen to provide adequate power (at least 90%) to detect the difference between etelcalcetide and placebo (using a 2-sided Chi-square test at a 5% significance level and assuming response rates for reducing PTH by > 30% from baseline of 35% for etelcalcetide and 20% for placebo). A Cochran-Mantel-Haenszel test stratified by randomization stratification factors was used in the analysis of the primary endpoint. Secondary efficacy endpoints were only tested for significance if the primary endpoint was significant (P<0.05). Efficacy analysis was based on the Full Analysis Set which included all randomized patients, and those patients with data missing during the EAP were considered to have not achieved the endpoint (i.e., non-responder imputation) [28, 29].

4.4.2 Active-controlled study comparing etelcalcetide with cinacalcet (Study 20120360): statistical analysis and study groups

The planned sample size of 600 was chosen to provide 90% power to demonstrate noninferiority for the primary endpoint using a margin of 12% for the upper bound of the 95% 2-sided confidence interval (CI) for the treatment difference between etelcalcetide and cinacalcet (cinacalcet minus etelcalcetide) and assuming response rates of 60% in each group. For the superiority testing, the study has more than 90% power to detect statistically significant differences on the endpoints of >50% reduction in PTH and mean number of days of vomiting or nausea, and more than 80% power for the endpoint of >30% reduction in PTH, assuming a 5% significance level, a 2-sided test, and response rates of [30]:

- 60% etelcalcetide and 45% cinacalcet for > 50% reduction in PTH
- 68% etelcalcetide and 57% cinacalcet for > 30% reduction in PTH
- 0.1 etelcalcetide and 0.57 cinacalcet for mean number of days of vomiting or nausea per week (common standard deviation of 1.48 assumed).

The primary endpoint analysis was based on a Mantel-Haenszel method, with missing data imputed using the non-inferiority null method. The pre-specified imputation method for the secondary endpoints of > 30% and > 50% reduction in PTH was non-responder imputation.

A comparison of the statistical aspects of the placebo- and active-controlled trial designs is provided in Table 12.

Table 12: Statistical aspects of the etelcalcetide phase 3 RCTs

Trial ID	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
20120229 [28] & 20120230 [29]	Etelcalcetide plus PB/VD would increase the proportion of subjects who had a reduction in PTH greater than 30% during the EAP, defined as weeks 20 to 27, inclusive), when compared with a treatment regimen consisting of PB/VD and placebo.	Descriptive statistics were used to summarize data for continuous variables (including n, mean, standard deviation [SD], or standard error, median, 25th [Q1] and 75th [Q3] percentiles, minimum and maximum values, and corresponding 95% confidence intervals [CIs], where applicable). For categorical variables, the number and percentage of subjects in each category were reported. Graphical presentation was provided for selected endpoints. To control for the study-wise Type 1 error rate, the secondary efficacy endpoints were tested only if the primary efficacy endpoint reached the prespecified 2 sided significance level of 0.05. If this occurred, the secondary efficacy endpoints were tested sequentially in the following order, each at a significance level of 0.05: ○ proportion of subjects with predialysis PTH ≤ 300 pg/mL; ○ percent change from baseline to EAP in PTH; ○ percent change from baseline to EAP in cCa; ○ percent change from baseline to EAP in cCa x P; ○ percent change from baseline to EAP in phosphorus.	A sample size of 250 in each treatment group would have at least 90% power to detect the treatment difference between etelcalcetide and placebo, with response rates of 35% and 20% for etelcalcetide and placebo, respectively, using a Chi-square test with a statistical significance level of 0.05 (2-sided). This calculation was based on response rates from a previous phase 2 study.	The difference in participant discontinuations (13.4% for etelcalcetide vs. 24.0% for placebo in 20120229; 14.5% for etelcalcetide vs. 21.5% for placebo in 20120230) was mainly because of a difference in the number of subjects who met the criteria for discontinuation after week 12 because of rising PTH (1 subject, (0.4%) for etelcalcetide vs. 29 subjects (11.4%) for placebo in 20120229; 1 subject (0.4%) for etelcalcetide vs. 25 subjects (9.6%) for placebo in 20120230). The full analysis set was used for the primary analyses for primary and secondary endpoints. This included all randomized subjects. Each subject was analysed according to the randomised treatment group. The safety analysis set was used for all safety endpoints. This included all subjects who were randomized and received at least 1 dose of investigational product. Subjects who received the incorrect treatment throughout the course of the study were analysed according to the treatment received. All other subjects were analysed according

Trial ID	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				to the randomized treatment group. The completer analysis set was used for sensitivity analyses. This was defined for the primary and each of the secondary efficacy endpoints. The completer analysis set included all randomised subjects with at least 1 scheduled predialysis lab concentration during the EAP for the corresponding endpoint. Subjects were analysed according to the randomized treatment group. Missing data were considered using last value carried forward and multiple imputations methods.
Amgen 20120360 [30]	Etelcalcetide is not inferior to cinacalcet as measured by the proportion of subjects with a > 30% reduction from baseline in mean predialysis serum PTH concentration during the EAP. Etelcalcetide is superior to cinacalcet as measured by the proportion of subjects with a > 50% decrease in predialysis serum PTH from baseline, by the proportion of subjects with a > 30% decrease in predialysis serum PTH from baseline, and by the mean number of days of vomiting or nausea per week during the first 8 weeks.	Continuous variables were summarized using descriptive statistics, including the number of observations, mean, SD, standard error (SE), median, the first and third quartiles (Q1, Q3), minimum, and maximum. Categorical variables were summarized using the number and percent of subjects. Etelcalcetide was considered noninferior if the upper bound of the 2-sided 95% CI of the treatment difference (cinacalcet – etelcalcetide) was smaller than 12%. If this criterion was met, the 3 key superiority secondary endpoints were tested	The planned sample size was 600 subjects (300 subjects per treatment arm). A non-inferiority margin was determined based on data collected in the Amgen EVOLVE Study. Rates in EVOLVE for 30% reductions in PTH from baseline were 60% and 25% in the cinacalcet and placebo arms, respectively. The 2-sided 95% confidence interval (CI) for the treatment difference (cinacalcet - placebo) was (31%, 39%); half of this lower limit is 15.5%. As 12% is < 15.5% and would represent a loss of effect that is clinically acceptable, 12% was selected as	Overall, 679 subjects (99.4%) received investigational product (Safety Analysis Set) and 581 subjects (85.1%) completed the study. Subject disposition was similar between treatment groups. 49/343 subjects in the cinacalcet group discontinued and 53/340 in the AMG 416 group. Full analysis set was used for the efficacy analyses, included all randomised subjects. Subjects were analysed according to treatment group assignment. Completer analysis set was used in the sensitivity analysis of the primary endpoint. This included

Trial ID	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		sequentially at the 5% significance level (2-sided). If all of the key secondary endpoints were also statistically significant, the other secondary endpoints were to be formally tested at an overall significance level of 0.05. The Hochberg approach was to be used to control the overall type I error.	the non-inferiority margin for this study. It was assumed that 60% of subjects randomized to each of the etelcalcetide and cinacalcet groups would achieve a > 30% reduction from baseline in mean predialysis PTH. Based on this assumption, 300 subjects per treatment group would provide 90% power to demonstrate non-inferiority using a margin of 12% for the upper bound of the 95% 2-sided CI for the treatment difference (cinacalcet – etelcalcetide). For the test of superiority based on the achievement of a > 50% or > 30% reduction from baseline in PTH, 300 subjects per treatment group would provide a > 90% or > 80% power, respectively, to detect a statistically significant treatment difference at the 5% significance level (2-sided). Response rates for > 50% reductions in PTH from baseline were assumed to be 60% and 45% and rates for > 30% reductions in PTH from baseline were assumed to be 68% and 57% for the AMG 416 and cinacalcet groups, respectively. Three hundred subjects per treatment group would also have a > 90% power to detect a treatment difference of 0.47 in the mean number of days of vomiting	all randomized subjects with at least 1 predialysis PTH value (including missing scheduled assessments replaced by unscheduled assessments) during the EAP. Subjects were analysed according to the randomized treatment group. Per protocol analysis set was used in the sensitivity analysis of the primary endpoint. This was defined as all randomized subjects who had no major protocol deviations, had at least 1 postdose PTH value, and had at least 16 weeks exposure of investigational product. Subjects were analysed according to the randomized treatment assignment. Safety analysis set was used for the safety analyses. This consisted of all randomized subjects who received at least 1 dose of investigational product. Subjects who received the incorrect treatment throughout the course of the study were analysed according to the treatment received. All other subjects were analysed according to the randomised treatment group. Safety analysis set with on-treatment approach was the same as the Safety Analysis Set except data collected on or before the

Trial ID	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
			or nausea per week in the first 8 weeks (mean of 0.57 for cinacalcet and 0.1 for AMG 416). This assumed the common standard deviation (SD) was 1.48 using a 2 group t-test with a 5% 2-sided significance level.	last non-missing dose of investigational product were summarized by visit. Missing values for non-inferiority analyses were imputed using noninferiority null method (performed 5 times). For superiority analyses missing values during the EAP were imputed as non-responders. A sensitivity analysis using multiple imputation was also used.

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 Patient disposition

Patient disposition in the three phase 3 RCTs is summarised in Table 13 and Figure 6, Figure 7 and Figure 8. Loss to follow-up was low (<6%) and over 80% of enrolled patients completed all three studies [28-30].

Across the two placebo-controlled studies (20120229 and 20120230) more patients in the placebo group than the etelcalcetide group discontinued from treatment (26% vs. 16%) and from the study (23% vs. 14%). The difference in discontinuation rates was due primarily to a larger percentage of placebo patients meeting the protocol criteria for study discontinuation after week 12 due to rising PTH (≥ 50% increase in PTH from baseline and PTH > 1000 pg/mL at 2 consecutive assessments at least 1 week apart). Discontinuations due to adverse events were low and similar for etelcalcetide and the comparators (see section 4.12). With the exception of discontinuation, patient disposition was similar between treatment groups [28, 29].

In the active-controlled study (20120360), patient disposition was broadly similar between treatment groups. Treatment discontinuation was similar for etelcalcetide and cinacalcet (20% vs. 18%), with a slightly higher percentage of patients discontinuing etelcalcetide to receive a kidney transplant (4.4% vs 1.5%, respectively) [30].

The most common reason for discontinuation from etelcalcetide in all three studies was patient request, which occurred at a similar incidence for the comparators [28-30].

Table 13. Patient disposition in the etelcalcetide RCTs

	Study 20120229		Study 20120230		Study 20120360	
	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet	Etelcalcetide
Efficacy population, n	254	254	260	255	343	340
[redacted]						
Discontinued from study, n (%)	61 (24.0)	34 (13.4)	56 (21.5)	37 (14.5)	49 (14.3)	53 (15.6)
Withdrawal of consent	15 (5.9)	12 (4.7)	12 (4.6)	12 (4.7)	32 (9.3)	31 (9.1)
Lost to follow-up	10 (3.9)	11 (4.3)	12 (4.6)	19 (7.5)	9 (2.6)	12 (3.5)
Death	7 (2.8)	9 (3.5)	7 (2.7)	5 (2.0)	6 (1.7)	10 (2.9)
Decision by sponsor	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)
Protocol specified criteria	29 (11.4)	1 (0.4)	25 (9.6)	1 (0.4)	0 (0.0)	0 (0.0)
Rising PTH criteria met	29 (11.4)	1 (0.4)	25 (9.6)	1 (0.4)	NA	NA

HD, haemodialysis; NA, not applicable; PTH, parathyroid hormone
Source: [redacted]

Figure 6: Study 20120229 patient disposition

[redacted]Figure 7: Study 2(

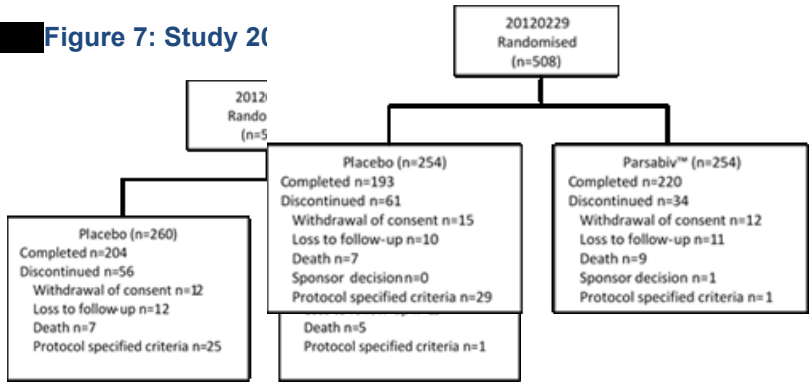
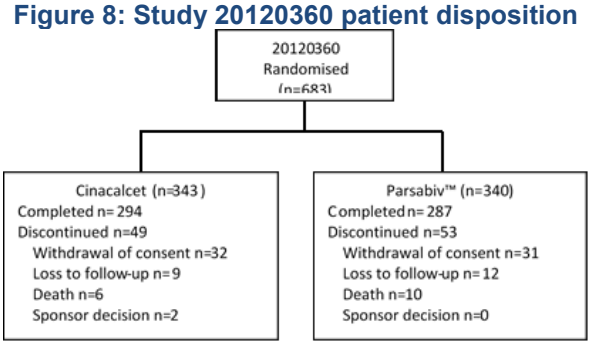


Figure 8: Study 20120360 patient disposition



4.5.2 Baseline characteristics

The baseline characteristics of enrolled patients were well balanced between treatment groups in all three phase 3 RCTs (Table 14).

In the placebo-controlled studies (20120229 and 20120230), which employed the same inclusion/exclusion criteria, baseline characteristics were similar within and between studies. Across the two placebo-controlled studies, 60% of patients were male and mean age was 58 years in both treatment groups. The majority of patients had baseline dialysate calcium ≥ 2.5 mEq/L and 88% had a dialysis vintage of more than 1 year. Patients were stratified according to screening PTH (33% PTH < 600 pg/mL, 46% PTH 600 to 1000 pg/mL, 21% PTH > 1000 pg/mL), region (54% North America, 46% non-North America), and recent cinacalcet use within 8 weeks before randomization (13% yes, 87% no). Median baseline PTH levels were around 700pg/mL, and 46% of patients enrolled across both RCTs had a prior history of cinacalcet use [28] [29].

In the active-controlled study (20120360), 56% of patients were male, mean age was 55 years, 45% had dialysate calcium ≥ 3.0 mEq/L and 86% had a dialysis vintage of more than 1 year. Patients were stratified according to screening PTH (50% PTH < 900 pg/mL, 50% PTH ≥ 900 pg/mL) and region (30% North America, 70% non-North America). Median baseline PTH levels were around 900pg/mL, and 25% had a history of prior cinacalcet use [30].

Table 14: Baseline characteristics of patients in the etelcalcetide RCTs

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

cCa, corrected calcium; cCa x P, corrected calcium-phosphorus product; ESRD, end-stage renal disease; P, phosphorus; PKD, polycystic kidney disease; PTH, parathyroid hormone; SD, standard deviation.
[a] includes Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Russian Federation, Spain, Sweden, Switzerland, Turkey, United Kingdom
[b] Categorization differs for 20120229/20120230 vs 20120360 due to difference in study eligibility criteria for dialysate calcium (≥ 2.25 vs ≥ 2.5 mEq/L, respectively)
Source: 20120229, 20120230, 20120360 clinical study reports [28] [29] [30]

4.6 *Quality assessment of the relevant randomised controlled trials*

In order to assess the risk of bias of the three phase 3 etelcalcetide RCTs, quality assessment was undertaken using the Cochrane collaboration 2011 checklist [78]. Full assessment of each trial is included in Appendix 4, and a summary of the assessments using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care' [79] is provided in Table 15.

In all three trials, randomisation and concealment of treatment allocation were appropriately conducted to prevent selection bias. Performance and detection bias were minimised by double-blinding and use of objective (rather than subjective) endpoints. Attrition bias was not a concern and randomisation was fully preserved: there were no unexpected differences in patient disposition, all patients were accounted for, and efficacy analyses were conducted on all randomised patients with appropriate methods for missing data. There was no selective reporting of outcomes or other obvious sources of bias. In summary, the three phase 3 etelcalcetide RCTs have high internal validity and their results are at a low risk of bias.

Assessment of the relevance of these trial data to UK clinical practice and how these data address the decision problem defined by the NICE scope is discussed in section 4.13.2.

Table 15: Summary of quality assessment of etelcalcetide RCTs

Element of bias assessment	Placebo-controlled trials 20120229 & 20120230	Active-controlled trial 20120360
Was randomisation carried out appropriately?	Yes – randomisation computer generated and appropriately stratified for severity, prior cinacalcet use and geographical location	Yes – randomisation computer generated and appropriately stratified for severity and geographical location
Was the concealment of treatment allocation adequate?	Yes - Interactive voice response system	Yes - Interactive voice response system
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – baseline characteristics well balanced, and stratified randomisation	Yes – baseline characteristics well balanced, and stratified randomisation
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – double-blind trial design	Yes – double-blind trial design
Were there any unexpected imbalances in drop-outs between groups?	No – a greater proportion of placebo recipients dropped out as met pre-specified criteria for study discontinuation after week 12 due to rising PTH (as would be expected). Otherwise, patient disposition was similar between groups.	No - patient disposition was similar between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – analyses included all randomised patients. Appropriate imputation methods used to account for missing data	Yes – analyses included all randomised patients. Appropriate imputation methods used to account for missing data

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 Outcomes and endpoints assessed in the RCTs

Table 16 summarises the outcomes and endpoints assessed in each RCT.

Table 16. Details of evidence presented from RCTs

	Outcomes presented
Study 20120229 (vs placebo) **Study 20120230 (vs placebo)** **Integrated analysis across placebo-controlled studies (pooled analysis)**	**Primary Endpoint (superiority)** Achievement of a > 30% reduction in mean PTH from baseline during EAP **Secondary Endpoints** Achievement of mean PTH ≤ 300 pg/mL during EAP, n (%) % change from baseline in mean PTH during EAP % change from baseline in mean cCa during EAP % change from baseline in mean cCa x P during EAP % change from baseline in mean P during EAP **Exploratory Outcomes** Reductions from baseline in fibroblast growth factor (FGF-23) Biochemical markers of high turnover bone disease, bone specific alkaline phosphatase (BSAP) and serum collagen type 1 cross-linked C-telopeptide (CTX), Time to First Occurrence of PTH > 30% Reduction From Baseline **Pre-specified covariate, subgroup analyses** **Post hoc analyses**
Study 20120360 (vs cinacalcet)	**Primary Endpoint (non-inferiority)** Achievement of a > 30% reduction in mean PTH from baseline during EAP **Secondary Endpoints (superiority)** Achievement of a > 50% reduction in mean PTH from baseline during EAP, n (%) Achievement of a > 30% reduction in mean PTH from baseline during EAP, n (%) Mean number of days of vomiting or nausea per week in the first 8 weeks % change from baseline in mean cCa during EAP Achievement of a mean pre-dialysis P ≤ 4.5 mg/dL during the EAP, n (%) Mean number of episodes of vomiting per week in the first 8 weeks Time to First Occurrence of PTH > 30% Reduction From Baseline **Prespecified covariate, subgroup analyses** **Post hoc analyses**

4.7.2 Efficacy results from placebo-controlled RCTs (20120229 and 20120230)

Results for the primary and secondary efficacy endpoints of the placebo-controlled phase 3 RCTs (studies 20120229 and 20120230) are summarised for each study and, given their similarity, integrated across studies, in Table 17. Etelcalcetide demonstrated clinically meaningful efficacy in and across both RCTs.

Table 17: Summary of results for the primary and secondary efficacy endpoints in the placebo-controlled phase 3 studies (20120229 and 20120230)

	Study 20120229		Study 20120230		Pooled	
	Placebo (N = 254)	Etelcalcetide (N = 254)	Placebo (N = 260)	Etelcalcetide (N = 255)	Placebo (N = 514)	Etelcalcetide (N = 509)
Primary endpoint:						
Achievement of a > 30% reduction in mean PTH from baseline during EAP, n (%)	21 (8.3)	188 (74.0)	25 (9.6)	192 (75.3)	46 (8.9)	380 (74.7)
Odds ratio[a] (95% CI) *P* value	32.46 (18.71, 56.31) <0.001		30.80 (18.18, 52.17) < 0.001		31.60 (21.59, 46.25) <0.001	
Secondary endpoints:						
Achievement of mean PTH ≤ 300 pg/mL during EAP, n (%)	13 (5.1)	126 (49.6)	12 (4.6)	136 (53.3)	25 (4.9)	262 (51.5)
Odds ratio[a] (95% CI)	22.08 (11.47, 42.48)		33.92 (16.35, 70.37)		27.02 (16.62, 43.93)	
P value	< 0.001		< 0.001		<0.001	
% change from baseline in mean PTH during EAP						
n	219	229	237	227	456	456
Mean (SE)	13.00 (2.81)	-55.11 (1.94)	13.72 (2.50)	-57.39 (1.91)	13.37 (1.87)	-56.25 (1.36)
Treatment difference, % Estimate (SE)	-71.11 (3.39)		-71.34 (3.15)		-71.30 (2.31)	
95% CI	-77.77, -64.46		-77.53, -65.14)		-75.84, -66.76	
P value	<0.001		< 0.001		<0.001	
% change from baseline in mean cCa during EAP						
n	219	229	237	227	456	456
Mean (SE)	1.18 (0.29)	-7.29 (0.53)	0.58 (0.29)	-6.69 (0.55)	0.87 (0.20)	-7.00 (0.39)
Treatment difference, % Estimate (SE)	-8.38 (0.58)		-7.20 (0.60)		-7.77 (0.42)	
95% CI	-9.52, -7.23		-8.38, -6.03		-8.60, -6.94	
P value	<0.001		< 0.001		< 0.001	
% change from baseline in mean cCa x P during EAP						
n	213	227	234	223	447	450
Mean (SE)	-0.19 (1.44)	-14.34 (2.06)	-1.06 (1.42)	-15.84 (1.57)	-0.64 (1.01)	-15.09 (1.30)
Treatment difference, % Estimate (SE)	-14.99 (2.41)		-14.58 (2.07)		-14.68 (1.59)	
95% CI	-19.73, -10.25		-18.65, -10.51		-17.81, -11.56	
P value	< 0.001		< 0.001		< 0.001	
% change from baseline in mean P during EAP						
n	214	227	234	223	448	450
Mean (SE)	-1.31 (1.42)	-7.71 (2.16)	-1.60 (1.42)	-9.63 (1.61)	-1.46 (1.00)	-8.66 (1.35)
Treatment difference, % Estimate (SE)	-7.45 (2.47)		-8.04 (2.09)		-7.59 (1.62)	
95% CI	-12.31, -2.59		-12.15, -3.92		-10.77, -4.40	
P value	0.003		< 0.001		< 0.001	

cCa, corrected serum calcium; CI, confidence interval; EAP, Efficacy Assessment Phase (weeks 20-27); n, number of patients with observed data; P, phosphate; PTH, parathyroid hormone; SE, standard error
[a] Cochran-Mantel-Haenszel (CMH) stratified odds ratio (etelcalcetide™:placebo). P value from CMH test.
Source: summary of clinical efficacy [31]

4.7.2.1 Primary endpoint – placebo-controlled RCTs

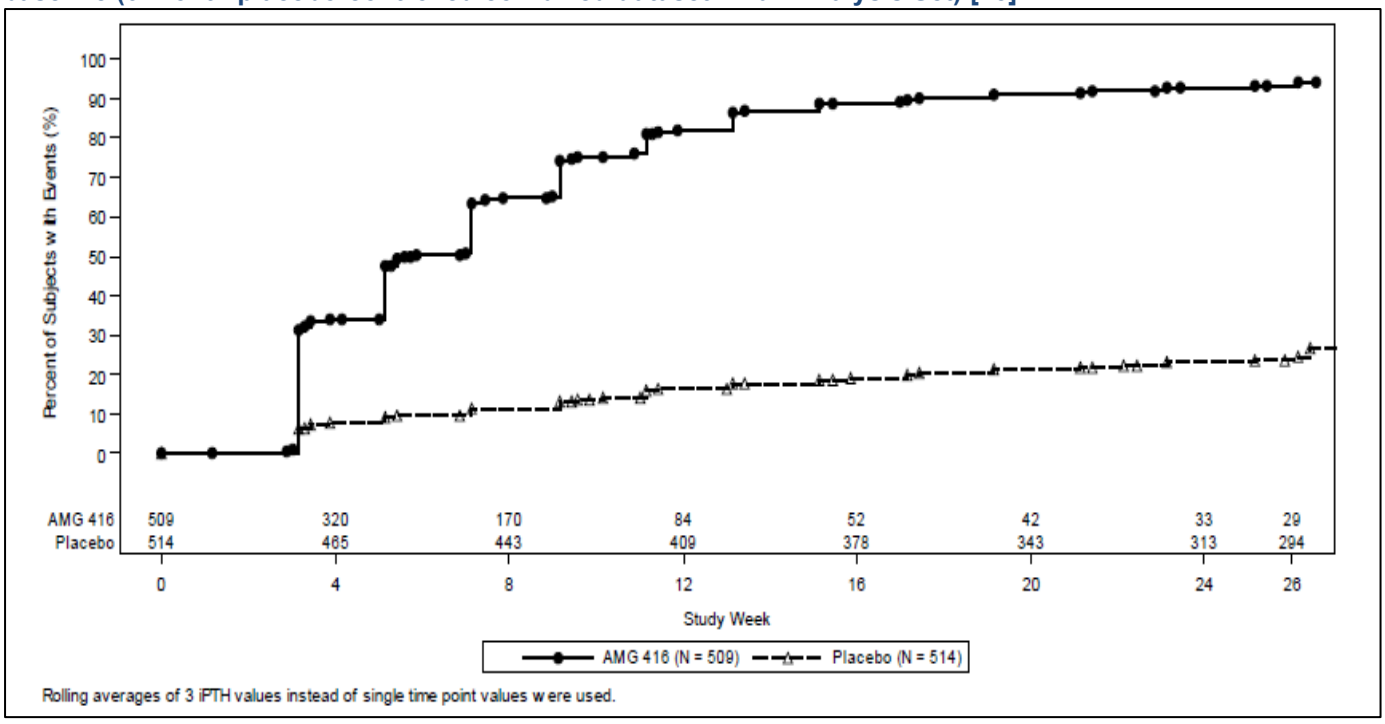
As discussed in section 4.4, results for the primary analysis are based on the full analysis set, which included all randomised patients.

In both studies individually, and in the integrated analysis, a similar significantly greater proportion of patients treated with etelcalcetide achieved the primary endpoint of >30% reduction from baseline in PTH during the EAP compared with placebo (integrated analysis: 74.7% vs. 8.9%; Odds ratio [OR] [95% CI]: 31.60 [21.59 to 46.25]; P<0.001; number needed to treat [NNT]: 2) [31].

Approximately 35% of subjects receiving etelcalcetide had > 30% reduction in PTH from baseline at week 4 (i.e., before the first dose titration) [31] (see Figure 9), indicating that etelcalcetide can provide rapid control PTH for many patients at the initial dose of 5mg three times per week. The most frequent dose remained 5mg three times per week throughout the studies [25].

As the primary end point was statistically significant, sequential testing of secondary endpoints could be undertaken [31].

Figure 9: Kaplan-Meier estimates of time to first occurrence of PTH > 30% reduction from baseline (6-month placebo-controlled combined dataset – Full Analysis Set) [25]



4.7.2.2 Secondary endpoints – placebo-controlled RCTs

Consistent with the primary endpoint, all secondary endpoints evaluated in each placebo-controlled RCTs achieved statistical significance after adjusting for multiplicity [31].

In the integrated analysis, the proportion of patients with mean PTH ≤ 300 pg/mL during the EAP was significantly higher for the etelcalcetide group compared with placebo (51.5% vs

4.9%; OR [95% CI]: 27.02 [16.62 to 43.93]; P<0.001; NNT: 2) [31]. As achievement of PTH ≤ 300 pg/mL in observational studies has been associated with a reduced risk of all-cause mortality compared with PTH values >300 pg/mL [46], and decreased bone turnover and improved bone histology [80], this finding supports the clinically meaningful efficacy of etelcalcetide in SHPT patients.

Treatment with etelcalcetide also resulted in statistically significant percent decreases from baseline in mean PTH, corrected calcium (cCa), corrected calcium-phosphate product (cCa x P) and phosphate (P) during the EAP compared with placebo (P<0.001) [31] (Table 17).

4.7.2.3 Exploratory analyses – placebo-controlled RCTs

Reductions from baseline in fibroblast growth factor (FGF-23) and biochemical markers of high turnover bone disease, bone specific alkaline phosphatase (BSAP) and serum collagen type 1 cross-linked C-telopeptide (CTX), were greater for etelcalcetide compared with placebo at week 27 [31]. Although only exploratory endpoints, these lend further support to a consistent clinically meaningful effect of etelcalcetide, given the association of these biochemical markers with adverse outcomes in patients with CKD [81] [82] [49].

[redacted] These data indicate that treatment with etelcalcetide must be continued to maintain beneficial effects, and highlight the importance of adherence and persistence with calcimimetic treatment.

4.7.3 Efficacy results from the active-controlled RCT (20120360)

Results for the primary and secondary efficacy endpoints of the active-controlled RCT comparing etelcalcetide with cinacalcet are presented in Table 18.

4.7.3.1 Primary endpoint (non-inferiority) – active-controlled RCT

The observed proportion of patients with a > 30% reduction from baseline in mean PTH during the EAP was higher in the etelcalcetide group (77.9%) compared with the cinacalcet group (63.9%) (Table 18). The estimated difference [95% CI] in the proportion of patients achieving the primary endpoint (cinacalcet minus etelcalcetide) was -10.48% [-17.45% to -3.51%], meeting the pre-specified criterion for non-inferiority [31].

As in the placebo-controlled trials, approximately 35% of subjects receiving etelcalcetide had >30% reduction in PTH from baseline at week 4 (i.e., before the first dose titration, at a dose of 5mg three times per week) [31] (Figure 10). Median weekly dose of etelcalcetide in the EAP was 15mg (equivalent to 5mg three times per week), and for cinacalcet was 360mg (equivalent to 51.4mg per day) [30].

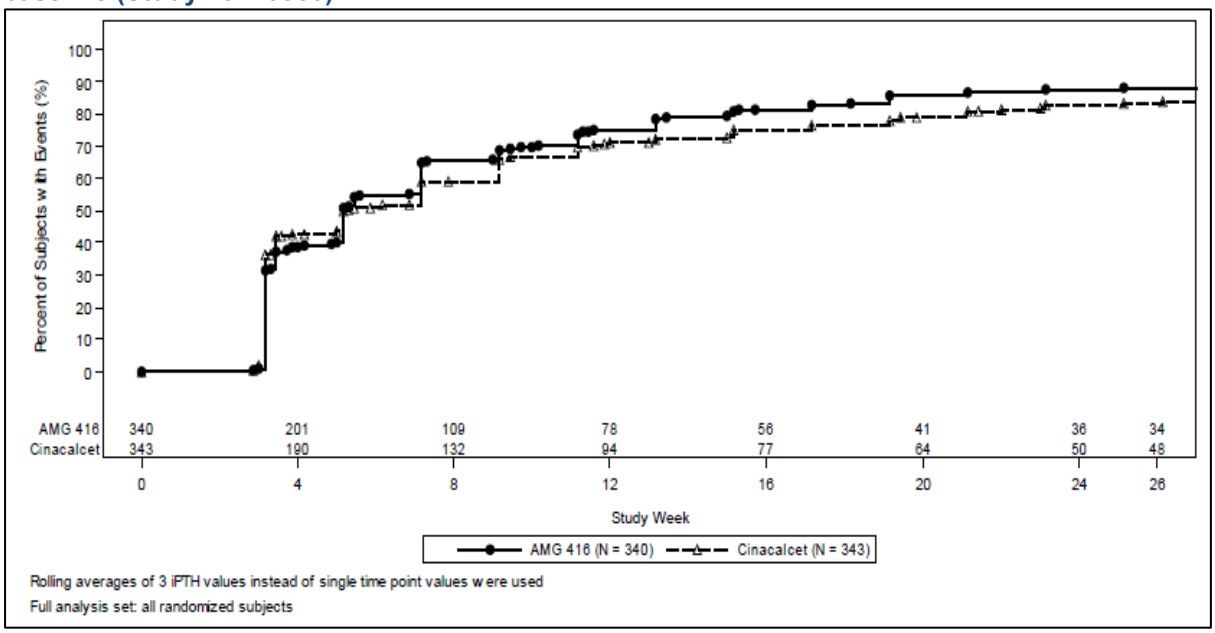
As non-inferiority had been demonstrated, sequential testing of the three key secondary endpoints to assess superiority of etelcalcetide over cinacalcet could therefore be undertaken [30].

Table 18: Summary of results for the primary and secondary efficacy endpoints in the active-controlled phase 3 study (20120360)

	Cinacalcet (N=343)	Etelcalcetide (N=340)
Primary Endpoint (Noninferiority)		
Achievement of a > 30% reduction in mean PTH from baseline during EAP[a], n/n1 (%)	198/310 (63.9)	232/298 (77.9)
Stratified treatment difference[b], % (95% CI)	-10.48 (-17.45, -3.51)	
Key Secondary Endpoints (Superiority)		
Achievement of a > 50% reduction in mean PTH from baseline during EAP[c], n (%)	138 (40.2)	178 (52.4)
Odds ratio (95% CI) (etelcalcetide:cinacalcet) P value	1.65 (1.21, 2.23) 0.001	
Achievement of a > 30% reduction in mean PTH from baseline during EAP[c], n (%)	198 (57.7)	232 (68.2)
Odds ratio (95% CI) (etelcalcetide:cinacalcet) P value	1.59 (1.16, 2.17) 0.004	
Mean number of days of vomiting or nausea per week in the first 8 weeks		
n	324	331
Adjusted mean (SE)	0.3 (0.03)	0.4 (0.04)
Treatment difference (rate ratio etelcalcetide:cinacalcet)		
Estimate (SE)	1.2 (0.15)	
95% CI	0.89, 1.49	
P value	0.27	
Other Secondary Endpoints		
% change from baseline in mean cCa during EAP		
n	310	298
Mean,% (SE)	-6.28 (0.44)	-9.83 (0.49)
Treatment difference, % (etelcalcetide-cinacalcet)		
Estimate (SE)	-3.48 (0.65)	
95% CI	-4.76, -2.21	
P value (descriptive)	<0.001	
Achievement of a mean pre-dialysis P ≤ 4.5 mg/dL during the EAP[c], n (%)	100 (29.2)	109 (32.1)
Odds ratio (95% CI)	1.15 (0.83, 1.59)	
P value (descriptive)	0.41	
Mean severity of nausea in the first 8 weeks		
n	339	339
Adjusted mean (SE)	0.48 (0.06)	0.45 (0.06)
Treatment difference (etelcalcetide-cinacalcet)		
Estimate (SE)	-0.03 (0.08)	
95% CI	-0.18, 0.12	
P value (descriptive)	0.71	
Mean number of episodes of vomiting per week in the first 8 weeks		
n	324	331
Adjusted mean (SE)	0.1 (0.02)	0.2 (0.02)
Treatment difference (rate ratio etelcalcetide:cinacalcet)		
Estimate (SE)	1.2 (0.22)	
95% CI	0.86, 1.72	
P value (descriptive)	0.26	

cCa, corrected calcium; CI, confidence interval; EAP, Efficacy Assessment Phase (weeks 20-27); n1, number of patients before imputation; P, phosphate; PTH, parathyroid hormone; SE, standard error
[a] Percentages reported are based on observed data without imputation
[b] Mantel-Haenszel estimator of the difference in proportions (cinacalcet - etelcalcetide). Missing data imputed using noninferiority null method (performed 5 times)
[c] Missing data imputed using non-responder imputation
Source: 20120360 clinical study report [30]

Figure 10: Kaplan-Meier estimates of time to first occurrence of PTH > 30% reduction from baseline (Study 20120360)



4.7.3.2 Key secondary endpoints (superiority) – active-controlled RCT

The proportion of patients with a > 50% reduction from baseline in mean PTH during the EAP was significantly greater in patients treated with etelcalcetide compared with cinacalcet (52.4% vs 40.2%; OR [95% CI]: 1.65 [1.21, 2.23]; P=0.001; NNT:8). Similarly, the proportion of patients with a > 30% reduction from baseline in mean PTH during the EAP was significantly greater in patients treated with etelcalcetide compared with cinacalcet (68.2% vs 57.7%; OR [95% CI]: 1.59 [1.16, 2.17]; P=0.004; NNT: 10) [30] (Table 18).

There was no difference between treatment groups in the mean number of days of vomiting or nausea per week in the first 8 weeks of treatment (adjusted mean [standard error (SE)]: 0.4 [0.04] vs. 0.3 [0.03] for etelcalcetide and cinacalcet, respectively; P=0.27) [30] (Table 18). Consequently, the remaining secondary endpoints were not formally tested for statistical significance; P-values for these and other endpoints are nominal only.

4.7.3.3 Other secondary endpoints – active-controlled RCT

Patients in the etelcalcetide group had a nominally significantly greater mean (SE) percent change from baseline in cCa during the EAP compared with those in the cinacalcet group (-9.83% [0.49%] vs -6.28% [0.44%]). Similar proportions of patients achieved a mean phosphate concentration ≤ 4.5 mg/dL during the EAP in the etelcalcetide and cinacalcet groups (32.1% vs 29.2%), and the mean severity of nausea and the mean number of episodes of vomiting per week in the first 8 weeks of treatment was also similar between the etelcalcetide and cinacalcet groups [30].

4.7.3.4 Exploratory endpoints – active-controlled RCT

Exploratory endpoints lend further support to the consistent clinically meaningful effects of etelcalcetide, as noted for the placebo-controlled RCTs.

[redacted].

Reductions from baseline in BSAP and CTX at week 27 were greater for etelcalcetide compared with cinacalcet (median change in BSAP: -7.13 vs -3.11 µg/L; median change in CTX -980 vs -490 ng/L). Similarly, a greater reduction in FGF-23 was observed for etelcalcetide compared with cinacalcet, with a median change from baseline to Week 27 of −1799 vs -608 pg/mL, respectively [30].

Over the first 16 and 26 weeks of treatment the mean number of episodes of vomiting per week and the mean severity of nausea per week were similar in the etelcalcetide and cinacalcet groups [30].

4.8 *Subgroup analysis*

4.8.1 Subgroup analyses of placebo-controlled trials

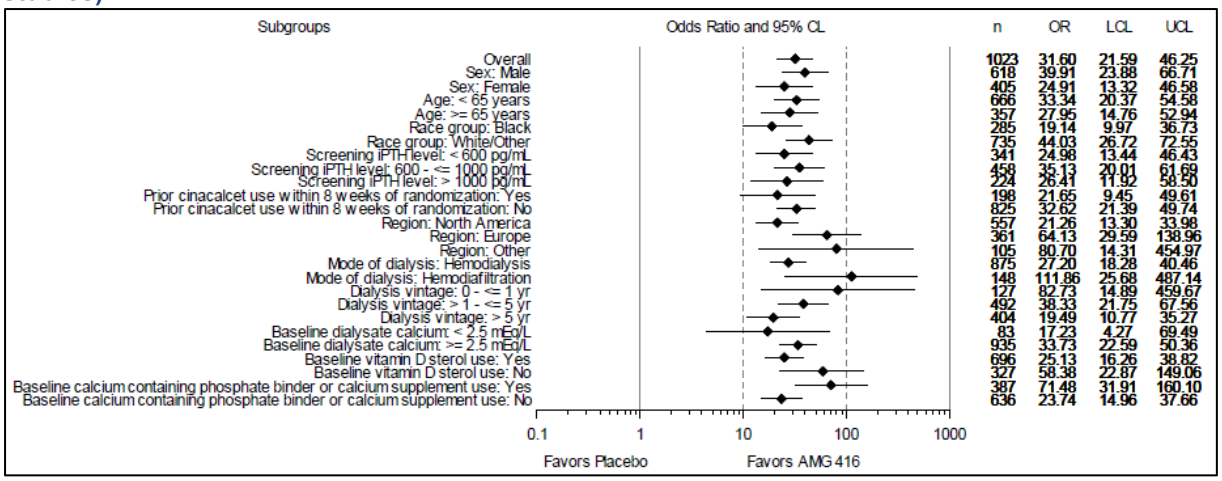
4.8.1.1 Pre-specified subgroup analyses – placebo-controlled RCTs

Etelcalcetide was significantly superior to placebo for the primary endpoint (>30% reduction from baseline in PTH) across all pre-defined baseline subgroups based on demographics, severity of SHPT and prior use of cinacalcet in both placebo-controlled trials [28, 29], and in the integrated analysis of these [31] (Figure 11).

[redacted]

The efficacy of etelcalcetide is therefore consistent, regardless of the baseline demographics, SHPT severity, and prior use of cinacalcet, indicating that etelcalcetide can be used across the broad range of patients with SHPT meeting its licensed indication in clinical practice.

Figure 11: Treatment difference in the proportion of patients with > 30% reduction from baseline in PTH during the EAP by subgroup (Pooled data from the placebo-controlled phase 3 studies)



OR, odds ratio for AMG 416:placebo; LCL, lower 95% confidence limit, UCL, upper 95% confidence limit
Note: AMG 416 refers to etelcalcetide.

[redacted]

4.8.1.2 Post hoc sub-group analyses – placebo-controlled RCTs – efficacy in cinacalcet discontinuations

The two phase 3 placebo-controlled etelcalcetide RCTs permitted enrolment of patients who had previously used cinacalcet. Across both trials, around 46% of participants had a history of cinacalcet use (see Table 14) [28, 29]xxxxxxxTable 19: Efficacy and safety of etelcalcetide following cinacalcet failure in placebo-controlled trials

[redacted]

4.8.2 Subgroup analyses of the active-controlled trial

[redacted]

[redacted]

4.9 *Meta-analysis*

Given their near-identical design and consistency of results across all endpoints, an integrated analysis of the placebo controlled RCTs (studies 20120229 and 20120230) was undertaken and submitted to the regulatory authority alongside the results of the individual trials [25]. Results of this integrated analysis are presented in section 4.7.2. Meta-analysis of the placebo-controlled and active-controlled etelcalcetide RCTs has not been conducted for this submission.

4.10 *Indirect and mixed treatment comparisons*

As direct comparative data for etelcalcetide and the comparators listed in the scope are available from high-quality, phase 3 RCTs, indirect and mixed treatment comparisons have not been undertaken for this submission.

4.11 *Non-randomised and non-controlled evidence*

The etelcalcetide clinical development programme included five non-controlled studies [31]. Of these, three are considered to provide relevant evidence to address the decision problem outlined in the scope: a single-arm switch study (20120359) [84] [85], and two large open-label extension studies of the three phase 3 etelcalcetide RCTs (studies 20120231 and 20130213) [32] [86] [33] (Table 20).

Table 20: Non-randomised / non-controlled etelcalcetide studies

Study ID/ Phase	Objective	Study Design	Dosage / Regimen	Number of Patients	Inclusion / Exclusion
20120331 Phase 2	Efficacy and safety	Multicentre, single-arm, multiple-dose, open-label, 12-week, dose titration study	5 mg starting dose with titration at wks 5 and 9 to max. 20 mg; administered as an IV bolus TIW at end of dialysis	37	Exclude: small dose titration study
20120334 extension Phase 2	Safety, tolerability, and efficacy	Multicentre, single-arm, open-label safety extension study to 20120331 parent study	2.5 to 15 mg administered as an IV bolus TIW at the end of dialysis for 40 weeks (extension period 1) with additional 2 years of open-label treatment (extension period 2).	30	Exclude: terminated early; small study, only 3 patients completed
20120359 Phase 3	Efficacy and safety	Multicentre, open label, multiple-dose, single-arm study to switch patients from oral cinacalcet to IV etelcalcetide	5 mg administered TIW for 4 weeks. Dose range 2.5 to 5 mg 7 days after discontinuing cinacalcet	158	Include: provides relevant information on efficacy of etelcalcetide in patients switching from cinacalcet
20120231 Phase 3	Safety, tolerability, and efficacy	Multicentre single-arm, 52-week extension study to parent studies 20120229, 20120230, and 20120359	5 mg starting dose to max 15 mg administered as an IV bolus TIW at the end of dialysis for 52 weeks	891	Include: large study providing relevant long term efficacy from key phase 3 RCTs
20130213 Phase 3	Safety and efficacy	Multicentre, single-arm, open label extension study to parent studies 20120360, 20120231, and 20120334	Identical dose to last dose in parent study or 2.5 mg for Study 20120360; administered as an IV bolus TIW at end of dialysis	902	Include: large study providing relevant long term efficacy from key phase 3 RCTs
IV = intravenous; TIW = three times a week					

4.11.1 Efficacy of etelcalcetide in patients switching from cinacalcet

A single arm, multi-centre, open-label, switch study was conducted to assess the safety and efficacy of etelcalcetide after cinacalcet therapy is discontinued in patients with CKD receiving haemodialysis (study 20120359). Patients on a stable daily oral dose of cinacalcet underwent a seven-day washout period before switching to etelcalcetide 5 mg three times per (provided that cCa was at least 8.3 mg/dL). Efficacy was a secondary endpoint, assessed by percent change in PTH from baseline (defined as after washout and prior to etelcalcetide initiation) during a 4-week treatment period [84] [85].

A total of 158 patients were enrolled, 148 completed the cinacalcet washout, and 147 were included in the Full Analysis Set (received at least one dose of drug and had at least 1 post-baseline serum corrected calcium value). Most were men (62.6%), approximately 46% were black and 44% were white, and mean age was 56.5 years. Most patients had a dialysis vintage > 5 years (57.8%), 11.6% had a history of kidney transplant and 4 patients (2.7%) had a parathyroidectomy. Before cinacalcet washout, 42.9% had received a daily cinacalcet dose of 30 mg, 32.0% had received a daily dose of 60 mg, and 23.8% had received a daily dose ≥ 90 mg [84].

Mean PTH decreased from baseline at each weekly time point: mean (SE) percent change in PTH from baseline was -3.9% (2.6%) at week 2, -7.8% (3.1%) at week 3, and -10.9% (2.9%) at week 4 [84]. These data indicate that etelcalcetide is efficacious in patients who switch from stable cinacalcet.

4.11.2 Long-term efficacy of etelcalcetide

The long-term efficacy and safety of etelcalcetide has been evaluated in a completed 52-week, phase 3, multicentre, single-arm, open-label extension study (Study 20120231; OLE1) [32] [86]. A further long-term extension study (Study 20130213; OLE2) is ongoing [33], with an interim analysis [87] described in section 4.11.2.2 below.

4.11.2.1 Open-label extension study 20120231 (OLE1)

OLE1 enrolled patients from the two placebo-controlled RCTs (20120229 and 20120230) and a single-arm switch study (20120359). All enrolled patients initiated etelcalcetide treatment at the 30-day follow-up visit of the parent studies, at a starting dose of 5 mg 3 times a week regardless of treatment they had received in the parent study. The dose of etelcalcetide could be titrated to a maximum dose of 15 mg to achieve target PTH levels ≤300 pg/mL while maintaining serum corrected calcium (cCa) concentrations. All subjects received PB/VD, as prescribed by the investigator. They were treated with etelcalcetide for up to 52 weeks, followed by a 30-day safety follow-up period unless they enrolled in a subsequent long-term follow-up study (Study 20130213; OLE2), in which case the 30-day safety follow-up period was postponed until the conclusion of that study. Efficacy assessments included changes from baseline in serum PTH, cCa, Phosphate (P) and cCa x P at 6 months (EAP6, weeks 20-26 inclusive), at 12 months (EAP12, weeks 46-53 inclusive) and during the last 6 weeks of treatment for those who completed at least 8 weeks of treatment (EAP) [32] [86]

A total of 891 patients were enrolled (768 from the placebo-controlled RCTs [20120229 and 20120230], and 123 from the single-arm switch study [20120359]). A total of 682 subjects (76.5%) completed the 52-week treatment period, and, 201 subjects (22.6%) completed both the 52-week treatment period and the 30-day safety follow-up period. Of the 687 subjects who discontinued the study before the 30-day safety follow up period, 476 discontinued because of protocol-specified criteria and rolled over into Study 20130213.

The majority of patients had a > 30% reduction from baseline in mean PTH when assessed in each efficacy assessment period: during EAP6 (68.1% of 742 subjects; 95% CI: 64.6% to

71.4%), during EAP12 (67.5% of 676 subjects; 95% CI: 63.8% to 71.0%), and during EAP (67.7% of 779 patients; 95% CI: 64.2% to 70.9%). In addition, over half of patients had PTH ≤300 pg/mL (Table 21) and mean PTH, cCa, cCa x P and P decreased from baseline during each efficacy assessment period [32] (Table 22). In summary, results from this study demonstrate that etelcalcetide efficacy is sustained, and continued reductions in PTH, calcium and phosphorus are observed, with long-term treatment [32] [86].

Table 21: Long-term PTH control with etelcalcetide in 52-week open-label extension study (20120231)

	>30% reduction from baseline PTH (%, 95%CI)	PTH ≤300pg/mL (%, 95%CI)
EAP6	68.1% (64.6% to 71.4%).	55.5% (52.0% to 59.1%)
EAP12	67.5% (63.8%, to71.0%)	56.4% (52.6% to 60.0%)
EAP	67.7% (64.2% to 70.9%)	57.3% (53.8% to 60.7%)
EAP6: the efficacy assessment phase at 6 months was defined as the period from week 20 to 26 (inclusive). EAP12: the efficacy assessment phase at 12 months was defined as the period from week 46 to 53 (inclusive). EAP: the efficacy assessment phase was defined as the last 6 weeks before ending treatment, which was only for subjects who completed a minimum of 8 weeks of treatment with etelcalcetide. Source: [32]		

Table 22: Long-term reduction in PTH, cCa and P in 52-week open-label extension study (20120231)

Percent change from baseline in:	Predialysis PTH	Predialysis cCa	Predialysis cCa x P	Predialysis Phosphorus
EAP6				
n	742	774	737	743
Mean (SE), %	-25.35 (6.03)	-9.10 (0.36)	-12.55 (1.28)	-4.07 (1.29)
Median, %	-51.57	-10.00	-17.55	-8.86
Q1, Q3, %	-74.80, -18.47	-16.00, -3.26	-34.78, 1.58	-25.42, 11.11
EAP12				
n	676	704	701	703
Mean (SE), %	-25.59 (4.59)	-8.25 (0.34)	-11.95 (1.13)	-3.59 (1.22)
Median, %	-52.94	-8.99	-15.60	-9.43
Q1, Q3, %	-72.54, -17.50	-14.76, -2.78	-30.98, 0.64	-22.96, 10.26
EAP				
n	779	807	786	796
Mean (SE), %	-26.07 (4.04)	-8.41 (0.34)	-12.04 (1.13)	-3.62 (1.20)
Median, %	-52.23	-9.52	-15.56	-7.91
Q1, Q3, %	-75.06, -15.56	-15.31, -2.47	-32.51, 3.33	-26.01, 12.40
cCa = corrected calcium; cCa x P = corrected calcium phosphorus product; CI = confidence interval; EAP = efficacy assessment phase; n = number of subjects with observed data in the analysis set; PTH = parathyroid hormone; SE = standard error. Baseline was the last assessment on or before study day 1 for 20120231. EAP6: the efficacy assessment phase at 6 months was defined as the period from week 20 to 26 (inclusive). EAP12: the efficacy assessment phase at 12 months was defined as the period from week 46 to 53 (inclusive). EAP: the efficacy assessment phase was defined as the last 6 weeks before ending treatment, which was only for subjects who completed a minimum of 8 weeks of treatment with etelcalcetide.				

4.11.2.2 Open-label extension study 20130213 (OLE2) – interim analysis summary

OLE2 is an ongoing single-arm, open-label extension study, designed as a follow-on to the OLE1 study above, to further characterise the long-term safety of etelcalcetide. Results are available from an interim analysis (data cut March 18, 2016) [33] [87].

Patients were enrolled from the OLE1 (20120231) study and from the phase 3 active-controlled etelcalcetide RCT (20120360). Those enrolled from OLE1 stayed on the same dose that they were on at the end of that study, whereas patients enrolled from the active-controlled RCT had a 4-week washout period before initiating etelcalcetide at a dose of 2.5mg three

times per week. Etelcalcetide was titrated (up or down) in 2.5 mg or 5 mg increments to a max of 15 mg to achieve PTH in the range between 2 to 9 times of the upper limit of normal, as recommended in clinical guidelines [11]. The primary endpoint was subject incidence of adverse events (AEs), with secondary endpoints of achievement of PTH in the target range and achievement of the phosphorus level below the upper limit of normal (P target) at months 6, 12, and 18 [87].

A total of 902 patients enrolled in the study. The mean time on drug during the study was 391 days, with follow-up available for 18 months in over 100 patients. No new safety concerns were observed. Results from the analyses of the secondary endpoints, as well as results from additional analyses characterising achievement of biochemical targets, are summarized in Table 23 [87].

Table 23: Summary of the biochemical target achievement in the 20130213 (OLE2) study (interim analysis)

Biochemical outcome	Month 6	Month 12	Month 18
PTH target (2 to 9 x ULN)	515/767 (67%)	424/591 (72%)	93/133 (70%)
P target	288/739 (39%)	197/533 (37%)	43/122 (35%)
PTH target AND P 3.5 - 5.5 mg/dL	211/716 (30%)	194/520 (37%)	34/110 (31%)
PTH target AND P 3.5 - 5.5 mg/dL AND normal corrected Ca	151/701 (22%)	154/516 (30%)	26/109 (24%)
PTH = parathyroid hormone; ULN=Upper limit of normal for the assay			

In summary, long-term treatment with etelcalcetide demonstrated sustained reductions in PTH and phosphorous using current clinical guideline recommended targets, with no new safety findings over long-term treatment of up to 18 months [87].

4.12 *Adverse reactions*

4.12.1 Safety profile in RCTs

RCT safety data is presented from the two placebo-controlled, double-blind, phase 3 trials (20120229 and 20120230 pooled) and the active-controlled, double-blind, double-dummy, phase 3 trial comparing etelcalcetide with cinacalcet (20120360). Collectively, these studies provide safety data from 1695 patients treated for up to 26 weeks (n=841 etelcalcetide, n=513 placebo, n=341 cinacalcet). Safety analyses are based on the Safety Analysis Set including all patients who received at least one dose of study drug. It should be noted that in the etelcalcetide clinical development programme asymptomatic laboratory findings of decreased calcium were classified as blood calcium decreased, and symptomatic events were classified as hypocalcaemia [34].

Overall, etelcalcetide was well tolerated, with an adverse event (AE) profile consistent with the pre-existing comorbid conditions typically associated with SHPT in patients with chronic kidney disease on haemodialysis and the mechanism of action of calcimimetics.

4.12.1.1 Overview of incidence of adverse events

In the placebo-controlled studies, a higher proportion of patients in the etelcalcetide group had treatment-emergent AEs compared with patients in the placebo group. However, the patient incidence of serious AEs, AEs leading to discontinuation of study drug, and fatal AEs, was not elevated for the etelcalcetide group compared with the placebo group [34]. In the active-controlled study, a similar proportion of patients in the etelcalcetide and cinacalcet groups had

treatment emergent AEs, serious AEs, and AEs leading to discontinuation of study drug. Fatal AEs occurred in 2.7% on etelcalcetide and 1.8% on cinacalcet; none of these were considered related to study drug [30] (Table 24).

Table 24: Overview of incidence of adverse events in etelcalcetide RCTs

	Total placebo-controlled studies		Study 20120360	
	Placebo (n=513)	Etelcalcetide (n=503)	Cinacalcet (n=341)	Etelcalcetide (n=338)
All treatment emergent AEs –n (%)	410 (79.9)	461 (91.7)	307 (90.0)	314 (92.9)
SAEs –n (%)	149 (29.0)	130 (25.8)	93 (27.3)	85 (25.1)
AEs leading to drug withdrawal –n (%)	13 (2.5)	9 (1.8)	16 (4.7)	19 (5.6)
Fatal AEs –n (%)	15 (2.9)	11 (2.2)	6 (1.8)	9 (2.7)
AEs=adverse events; SAE=serious adverse events Source: summary of clinical safety [34].; 20120360 CSR [30]				

4.12.1.2 Incidence of common adverse events (≥10% in the etelcalcetide group)

The most common AE in the placebo-controlled and active-controlled studies was decreased blood calcium, an expected physiological response to reductions in PTH associated with calcimimetic treatment (placebo-controlled studies: 63.8% etelcalcetide, 10.1% placebo; active-controlled study: 68.9% etelcalcetide, 59.8% cinacalcet). Other common AEs (≥10% in the etelcalcetide group) in the placebo-controlled studies were muscle spasms (11.5% etelcalcetide; 6.6% placebo), nausea (10.7% etelcalcetide; 6.2% placebo), and diarrhoea (10.7% etelcalcetide; 8.6% placebo). Other common AEs in the active-controlled study were nausea (18.3% etelcalcetide; 22.6% cinacalcet) and vomiting (13.3% etelcalcetide; 13.8% cinacalcet) [34].

4.12.1.3 Incidence of adverse events occurring with greater frequency with etelcalcetide compared with placebo or cinacalcet

AEs that occurred with a greater frequency in the etelcalcetide group compared with the placebo or cinacalcet group (≥ 5% in the etelcalcetide group with ≥ 1% difference from placebo or cinacalcet) are summarised in Table 25. The patient incidence of decreased blood calcium and hypocalcaemia was higher among patients who received etelcalcetide compared with placebo or cinacalcet. Most of these events were mild or moderate in severity and rarely led to permanent discontinuation of etelcalcetide; 5 (1%) patients in the etelcalcetide arm permanently discontinued due to decreased blood calcium or hypocalcaemia in the placebo-controlled studies [25] and no patients in the etelcalcetide arm permanently discontinued due to either event in the active-controlled study [30]. About 23-36% of patients on etelcalcetide temporarily discontinued treatment due to low serum calcium levels [25]. One serious AE of decreased blood calcium was reported in the etelcalcetide arm of the active-controlled study; however, this event was confounded by co-administration of another product known to reduce serum calcium. No serious AEs of hypocalcaemia were reported in any of the three RCTs [34].

Consistent with the higher patient incidence of hypocalcaemia, the rates of events potentially associated with increased neuromuscular irritability secondary to low calcium were also higher in the etelcalcetide group compared with placebo and mainly consisted of paraesthesia (4.8% etelcalcetide, 0.6% placebo), hypoesthesia (1.8% etelcalcetide, 0.8% placebo), and myalgia (1.6% etelcalcetide, 0.2% placebo) [88].

Other AEs occurring with a greater frequency in the etelcalcetide group compared with the placebo group included muscle spasms, diarrhoea, nausea, vomiting and headache. In the

active-controlled study, hypotension was reported more frequently for etelcalcetide compared with cinacalcet (6.8% etelcalcetide, 2.9% cinacalcet); however, the patient incidence of this event was similar for etelcalcetide and placebo in the placebo-controlled studies (6.0% etelcalcetide, 5.1% placebo) [34].

Table 25: Patient incidence of AEs occurring in ≥ 5% of patients in the etelcalcetide group with ≥ 1% difference from placebo or cinacalcet in phase 3 RCTs

	Total placebo-controlled studies		Study 20120360	
Preferred term	Placebo, % (N = 513)	Etelcalcetide % (N = 503)	Cinacalcet, % (N = 341)	Etelcalcetide % (N = 338)
Blood calcium decreased (asymptomatic)[a]	10.1	63.8	59.8	68.9
Muscle spasms	6.6	11.5	5.9	6.5
Diarrhoea	8.6	10.7	10.3	6.2
Nausea	6.2	10.7	22.6	18.3
Vomiting	5.1	8.9	13.8	13.3
Headache	6.0	7.6	7.0	6.5
Hypocalcaemia (symptomatic)[b]	0.2	7.0	2.3	5.0
Hypotension	5.1	6.0	2.9	6.8

AE, adverse event
[a] asymptomatic reduction in serum corrected calcium below 7.5 mg/dL or asymptomatic reduction in serum corrected calcium between 7.5 and < 8.3 mg/dL requiring medical management or deemed clinically significant by the investigator
[b] symptomatic reduction in serum corrected calcium < 8.3 mg/dL
Source: summary of clinical safety [34]

4.12.1.4 Incidence of adverse events of special interest

Certain categories of AEs were predefined as of special interest based on the mechanism of action and pharmacological profile of etelcalcetide, potential CaSR class effects and observations made during the nonclinical and clinical program. The patient incidence of these AEs of interest in the three phase 3 RCTs is summarized in Table 26.

The patient incidence of hypocalcaemia events of interest was higher for etelcalcetide (65.6%) compared with placebo (10.3%) in the placebo-controlled studies and for etelcalcetide (71.0%) compared with cinacalcet (60.7%) in the active-controlled study, with most events mild or moderate in severity. Electrocardiogram analysis in the placebo-controlled RCTs indicated that the etelcalcetide group had a higher patient incidence of post-baseline increases in corrected QT (QTc) interval compared with the placebo group, as would be anticipated for a therapeutic that reduces serum calcium; however, no evidence of an increased patient incidence in AEs potentially associated with QTc interval prolongation was observed among patients receiving etelcalcetide compared with those receiving placebo [34].

The patient incidence of hypersensitivity events of interest was similar between treatment arms in all studies. In the active-controlled study, a higher proportion of patients in the etelcalcetide arm had infusion reaction events (20.1% etelcalcetide; 15.5% cinacalcet); in the placebo-controlled studies 19.7% of patients in the etelcalcetide arm and 17.7% of patients in the placebo arm experienced these events. In all studies, the patient incidence of infusion reaction events was primarily driven by events such as hypertension, hypotension, and pyrexia, which are commonly observed in the CKD population. No association was noted between exposure to etelcalcetide and the occurrence of infusion-type reactions [34].

Cardiac failure events were pre-specified as events of interest since reductions in PTH with etelcalcetide can lower serum calcium, which could potentially worsen heart failure. In addition, cardiovascular events (myocardial infarction, stroke, and congestive heart failure

requiring hospitalisation) were reviewed and adjudicated by an independent event adjudication committee in the placebo-controlled studies. The patient incidence of adjudicated congestive heart failure requiring hospitalisation in the placebo-controlled studies was slightly higher in the etelcalcetide treatment group (2.2% etelcalcetide; 1.2% placebo) [88]. This was consistent with a slightly higher patient incidence of cardiac failure events of interest in the etelcalcetide group compared with placebo (3.2% etelcalcetide, 2.5% placebo) and compared with cinacalcet (3.0% etelcalcetide, 0.6% cinacalcet) (Table 26). Although some numerical differences were noted in the patient incidence of cardiac failure events of interest in the etelcalcetide arm compared to placebo and cinacalcet, the rate was consistent with the background rate of 3.3% in the placebo arm during the first 6 months of the EVOLVE study, a large cinacalcet cardiovascular outcomes study conducted in patients with chronic kidney disease on dialysis. No pattern of temporal associations of cardiac failure cases with etelcalcetide exposure was observed in the placebo-controlled or the active-controlled study [88].

Increases in potassium were not pre-specified as AEs of interest; however, an imbalance in these events was noted after review of the placebo-controlled RCT data. Although the rate of hyperkalaemia was higher in the etelcalcetide group (4.4%) compared with placebo (2.1%), the difference between groups was diminished when events of blood potassium increased were also included (4.4% etelcalcetide; 3.1% placebo) [34]. Detailed review of serious hypokalaemia events showed no consistent risk factors or associated events. Patient incidence rates for hyperkalaemia were similar between treatment arms in the active-controlled study (4.4% cinacalcet, 3.8% etelcalcetide) [34].

Table 26: Summary of patient incidence of AEs of interest in phase 3 RCTs

	Total placebo-controlled studies		Study 20120360	
Event of interest category, n (%)	Placebo (N = 513)	Etelcalcetide (N = 503)	Cinacalcet (N = 341)	Etelcalcetide (N = 338)
Adynamic bone	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac failure	13 (2.5)	16 (3.2)	2 (0.6)	10 (3.0)
Convulsions	5 (1.0)	4 (0.8)	2 (0.6)	3 (0.9)
Hypersensitivity	19 (3.7)	22 (4.4)	17 (5.0)	19 (5.6)
Hypocalcemia[a]	53 (10.3)	330 (65.6)	207 (60.7)	240 (71.0)
Hypophosphatemia	2 (0.4)	7 (1.4)	3 (0.9)	5 (1.5)
Infusion reaction	91 (17.7)	99 (19.7)	53 (15.5)	68 (20.1)
Torsade de pointes-QT prolongation	3 (0.6)	6 (1.2)	0 (0)	1 (0.3)
Ventricular tachyarrhythmias	4 (0.8)	2 (0.4)	0 (0)	0 (0)

AE, adverse event
[a] Includes the following preferred terms: blood calcium decreased, hypocalcaemia, adjusted calcium decreased and Chvostek's sign
Source: summary of clinical safety [34]

4.12.1.5 Other safety endpoints

Etelcalcetide had no clinically significant effects on vital signs, blood pressure, heart rate, or haematological laboratory parameters. Anti-etelcalcetide antibodies were observed in 56 (11%) of 503 patients receiving etelcalcetide in the placebo-controlled studies with 43 patients having detectable pre-existing anti-etelcalcetide antibodies. The presence of anti-drug binding antibodies did not impact pharmacokinetic exposure, safety (e.g., hypersensitivity and infusion reaction adverse events) or efficacy (reduction in PTH) of etelcalcetide [34].

4.12.2 Long-term safety of etelcalcetide

The long-term safety of etelcalcetide has been evaluated in a phase 3, open-label extension study (20120231) [32], which enrolled patients from the two etelcalcetide placebo-controlled trials and from a single-arm switch study (20120359).

In the safety set a total of 878 subjects received etelcalcetide, with a mean (SD) duration of exposure of 300.1 (94.3) days. The most common adverse event was blood calcium decreased (43.3%; 69.1 per 100 patient-years) but these were typically mild-to-moderate and transient. The most frequently reported serious adverse events (≥2% of subjects) were hyperkalaemia (3.3%; 3.5 per 100 patient-years) and cardiac failure congestive (2.0%; 2.2 per 100 patient-years). Decreases in calcium and phosphorus are known effects of etelcalcetide administration, and increases in potassium are a frequent occurrence in subjects receiving dialysis because of end-stage renal disease [32].

Additional events included diarrhoea (10.8%; 12.2 per 100 patient-years) and vomiting (10.4%; 11.8 per 100 patient-years). [redacted] Overall, results from this study demonstrate that etelcalcetide is well tolerated during long-term treatment. No new safety findings were observed with long-term treatment in this study, and there was no apparent increase in either the incidence or severity of events of interest over time [32].

4.12.3 Safety of etelcalcetide when switching from cinacalcet

The safety of etelcalcetide in patients who have discontinued cinacalcet therapy was evaluated in study 20120359 where patients on a stable daily oral dose of cinacalcet were switched to 5 mg etelcalcetide TIW for 4 weeks (see section 4.11.1). Safety endpoints included the incidence of cCa values < 7.5 mg/dL, the incidence of cCa values < 8.3 mg/dL, adverse events, and the incidence of symptomatic hypocalcaemia [84].

Of the 147 patients in the Full Analysis Set, one patient (0.7%) had cCa < 7.5 mg/dL, and 23 patients (15.6%) had cCa < 8.3 mg/dL during the 4-week treatment period [84]. Of the 148 patients in the Safety Analysis Set, 48.6% reported AEs and 11.5% had serious AEs. The most common AE was decreased blood calcium (3.4% of patients). Two patients (1.4%) had AEs leading to discontinuation of etelcalcetide and one patient had a fatal AE during the study (biliary sepsis) that was not considered treatment-related by the investigator. No patients had an AE of symptomatic hypocalcaemia at any time during the treatment period [84]. These data indicate that treatment with etelcalcetide at a starting dose of 5 mg can be safely initiated after a 7-day discontinuation of cinacalcet.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 Conclusions from the clinical evidence

Data from three robust phase 3 RCTs indicate that etelcalcetide administered intravenously by healthcare professionals three times per week at routine haemodialysis sessions provides superior SHPT control over placebo and daily oral cinacalcet when added to PB/VD regimens. Reductions in the key biochemical parameters used to guide treatment in practice (i.e., PTH, cCa, P) are consistent across the broad spectrum of SHPT patients in practice, including all subgroups defined by severity of SHPT and those who have previously been treated with cinacalcet (representative of patients refractory to PB/VD regimens alone). Open-label extension studies confirm the effects with etelcalcetide are maintained over the long-term (up to 18 months). Etelcalcetide is well tolerated, with an adverse event profile consistent with the pre-existing comorbid conditions typically associated with SHPT in patients with chronic kidney disease on haemodialysis and the mechanism of action of calcimimetics. The safety profile of etelcalcetide is similar to cinacalcet.

- In placebo-controlled trials, etelcalcetide significantly reduced PTH levels relative to placebo as measured by achievement of a clinically relevant >30% reduction in mean PTH from baseline, mean PTH ≤ 300 pg/mL, and percent change in mean PTH from baseline during the EAP (weeks 20-27). Significant percent reductions from baseline in mean cCa, P and cCa x P were also observed for etelcalcetide compared with placebo during the EAP [28, 29].
- In the active-controlled trial, etelcalcetide demonstrated superiority over cinacalcet for both the achievement of a > 30% and > 50% reduction in mean PTH from baseline during the EAP (weeks 20-27) [30]. This superior efficacy was achieved despite greater persistence to cinacalcet in the trial than is observed in clinical practice.
- Results were consistent irrespective of patient demographics, severity of SHPT, dialysis vintage, and prior use of cinacalcet [30, 31].
- Overall, etelcalcetide was well tolerated, with an adverse event profile consistent with the mechanism of action of calcimimetics. The patient incidence of decreased blood calcium and symptomatic hypocalcaemia was higher among patients who received etelcalcetide compared with placebo or cinacalcet; however, these events were mild or moderate in severity, are readily manageable, and rarely led to permanent discontinuation of etelcalcetide [34].
- Extension studies, providing up to 18 months of follow-up data for patients enrolled in RCTs, show that the efficacy and safety of etelcalcetide are maintained with long-term treatment [32, 33].
- Phase 3 trial data on etelcalcetide use in patients who have discontinued from stable cinacalcet dosing indicate that treatment with etelcalcetide at a starting dose of 5 mg reduces PTH and can be safely initiated after a 7-day discontinuation of cinacalcet [84]. This supports its use in patients switching from cinacalcet.
- Post hoc analyses of the phase 3 placebo-controlled trials suggest etelcalcetide is similarly effective and safe in those who discontinued cinacalcet due to lack of efficacy, adverse reactions or intolerability [83].

4.13.2 Relevance to evidence to clinical practice

The three phase 3 etelcalcetide RCTs enrolled a broad population of dialysis patients with SHPT in clinical practice, used etelcalcetide and the comparators as they would be used in clinical practice, and assessed outcomes that are relevant to clinical practice. In summary, the three phase 3 etelcalcetide RCTs have high external validity, and there is no reason to expect the treatment effects of etelcalcetide observed in the trials would differ markedly in clinical practice in the UK. However, it is plausible that the relative treatment effects of etelcalcetide compared with cinacalcet are underestimated in the active-controlled 20120360 study, as patient adherence and persistence with cinacalcet was greater than is typically observed in non-trial settings.

4.13.2.1 **Patient populations**

The trial inclusion/exclusion criteria (see Table 11) ensured that patients enrolled in the trials were broadly representative of the dialysis population with SHPT anticipated to be candidates for treatment with etelcalcetide in practice. This included patients who were calcimimetic-naïve, and those with prior cinacalcet use suggesting a history of being refractory to PB/VD regimens alone. Children (<18 years old) and pregnant patients were not included, but the eligibility criteria did not exclude any other important segments of the relevant population. Therefore, patient demographics are representative of the broad dialysis population with SHPT, as reflected in the baseline characteristics in section 4.5.2. As the trials enrolled patients from the US, Canada, East and West Europe, the Russian Federation, Australia and

New Zealand, results can be extrapolated globally. In summary, there is no reason to expect the treatment effects observed in the etelcalcetide trial populations would differ markedly in patients meeting its licensed indication in clinical practice in the UK, including those who are refractory to treatment with phosphate binder and vitamin D regimens alone.

4.13.2.2 Intervention and comparators

Etelcalcetide and cinacalcet were added to a background of PB/VD in the phase 3 trials, as would be expected in clinical practice, and were dosed and titrated in line with the recommendations in their Summary of Product Characteristics [23] [40]. Of note, doses were titrated to target a PTH level ≤300pg/mL. However, current PTH targets in practice are less stringent following revised clinical guideline recommendations (2 to 9 times upper limit of normal for the assay [11], with 9 times the upper limit of normal approximately equivalent to 600pg/mL [89]). Therefore, the calcimimetic drug doses used in the trials may exceed those that will be required to achieve current recommended PTH levels.

In addition, adherence and persistence with cinacalcet treatment in the active-controlled trial was higher than has been observed in clinical practice for this oral medication (86% completed 26 weeks of treatment in study 20120360 [30], compared with rates as low as 40% remaining on therapy at 6 months in real world data [90]), which may plausibly lead to an underestimate of the relative treatment effects for clinician-administered etelcalcetide compared with daily oral, patient-administered cinacalcet in clinical practice.

4.13.2.3 Outcomes

The internationally respected KDIGO clinical guidelines indicate the aim of SHPT treatment is to maintain PTH within an acceptable target range to attenuate the important clinical consequences of SHPT and the accompanying calcium and phosphate disturbances [11]. These biochemical parameters, which are used to guide treatment decisions and management of SHPT in clinical practice, were used to assess the efficacy and safety of etelcalcetide in the phase 3 RCTs.

The primary endpoint for all three etelcalcetide RCTs was achievement of a > 30% reduction in PTH from baseline during the EAP, defined as weeks 20 to 27 inclusive [28-30]. A > 30% reduction in PTH was also the primary endpoint in the registration studies for vitamin D sterols [31] and a secondary endpoint in the registration studies for cinacalcet in SHPT, and the CHMP considered this to be a relevant and clinically meaningful endpoint in the SHPT population [25]. Other pre-specified endpoints in the etelcalcetide RCTs are also clinically relevant, and included proportion of patients achieving PTH ≤300pg/mL and percentage change from baseline in pre-dialysis PTH, serum corrected calcium and serum phosphate concentrations during the EAP.

Although the impact of etelcalcetide on clinical events such as fracture, CV events and deaths has not been evaluated directly in RCTs, the link between elevated PTH and the risk of clinical events is well established, as is the change in the clinical course of SHPT when PTH, along with calcium and phosphate, is more effectively controlled (see section 3.1.2.1). In summary, the etelcalcetide RCTs assessed the most clinically relevant outcomes for the management of SHPT in clinical practice.

4.13.3 Relevance of evidence to address the decision problem defined by the NICE scope

As discussed in section 4.13.2, the three phase 3 etelcalcetide RCTs enrolled patients who were broadly representative of dialysis patients with SHPT anticipated to use etelcalcetide in clinical practice, they employed etelcalcetide and comparator treatment regimens and dosing algorithms as they would be used in clinical practice, and they assessed outcomes that are relevant to the management of SHPT in clinical practice. The RCTs were well designed and well conducted, and had high internal validity (section 4.6). Evidence from these RCTs is consistent, biologically plausible, robust and at low risk of bias.

The NICE Scope requested comparisons of etelcalcetide against [22]:

- Established clinical practice without calcimimetics (dietary modification to restrict phosphate, phosphate binders, analogues of vitamin D)
- For people with refractory secondary hyperparathyroidism: cinacalcet.

The two phase 3 placebo-controlled trials (studies 20120229 and 20120230) provide comparisons of etelcalcetide (added to background PB/VD) against PB/VD alone (defined in the NICE scope as established clinical practice without calcimimetics). Patients enrolled in these trials were stratified by baseline PTH, with 33% having PTH < 600 pg/mL, 46% PTH 600 to 1000 pg/mL, and 21% PTH > 1000 pg/mL. Results across the primary and secondary endpoints were consistent in each of these and all other pre-specified subgroups (including patient demographics, dialysis vintage, and prior cinacalcet use), confirming that etelcalcetide is a highly effective and safe treatment for SHPT across the broad population of SHPT patients meeting its licensed indication.

For the comparison against cinacalcet in people with refractory SHPT, a specific definition of refractory SHPT is not available; however, the phase 3 etelcalcetide RCTs permitted enrollment of calcimimetic-naïve patients and patients with prior cinacalcet use. Given that cinacalcet is typically used as an add-on to PB/VD in patients who are refractory to these regimens alone (see section 3.3.2), patients with a history of prior cinacalcet use that were enrolled in the etelcalcetide trials (46% of patients in the placebo-controlled and 25% of patients in the active-controlled RCTs) are highly likely to be representative of patients with a history of SHPT that is refractory to PB/VD alone. Etelcalcetide provided similar superior efficacy over cinacalcet in reducing PTH levels across all pre-specified subgroups, which included patient demographics, dialysis vintage, SHPT severity and prior cinacalcet use, confirming that etelcalcetide is similarly superior to cinacalcet across its whole licensed indication, and in specific subgroups representative of patients with SHPT that is refractory to PB/VD alone.

In summary, the three phase 3 etelcalcetide RCTs have high external validity, and results are highly generalisable to the broad population of SHPT patients meeting the etelcalcetide licensed indication in clinical practice, including those with SHPT that is refractory to PB/VD alone. Supported by the longer-term, open-label extension studies, they provide the most robust evidence possible to address the decision problem outlined in the NICE scope.

4.13.4 Strengths and limitations of the clinical evidence base

The clinical evidence base for etelcalcetide is derived from three large, international, well-designed, phase 3 RCTs, which provide the highest quality of evidence for presenting and evaluating clinical efficacy. These include two parallel, double-blind, placebo-controlled RCTs that compare etelcalcetide (as an add-on to PB/VD therapies) with PB/VD regimens alone, and a further direct comparative, double-blind, double-dummy RCT of etelcalcetide vs. cinacalcet (both added to PB/VD therapies). The clinical programme was based on the patient population for which a license was sought, which reflects the broad haemodialysis population with SHPT in clinical practice, and includes all relevant comparator therapies. Endpoints were

clinically meaningful, reflecting how SHPT, and response to SHPT treatment, is assessed in clinical practice. The primary endpoint for all three RCTs was achievement of a > 30% reduction in PTH from baseline during the EAP, which was the primary endpoint in the registration studies for vitamin D sterols, was a secondary endpoint in the registration studies for cinacalcet in SHPT, and was recognised by the CHMP as a clinically relevant and meaningful endpoint in this patient population [25]. Loss to follow-up rates were low, and exposure to etelcalcetide was adequately assessed at all dose levels to be used clinically. The trials were robust, with high internal validity, and results are at low risk of bias and are highly generalisable at patients in clinical practice.

A limitation of the clinical evidence base for etelcalcetide is that there are currently no real world data evaluating effectiveness in routine clinical practice. While improved adherence and persistence is expected for etelcalcetide over cinacalcet, based on the healthcare professional-controlled IV route of administration at the end of haemodialysis, it has not been tested in the real world setting; in the clinical trial setting persistence was comparable in cinacalcet and etelcalcetide patients, likely due to the increased persistence to oral medications typically observed in a controlled trial environment. Finally, although clinically relevant in practice, the effects of etelcalcetide have been assessed on biochemical endpoints, rather than clinical events such as fracture, cardiovascular events and deaths. However, as noted in section 3, the link between elevated PTH and the risk of clinical events is well established, as is the change in the clinical course of SHPT when PTH, along with other biomarkers, is more effectively controlled. The EVOLVE trial demonstrated that the risks of these events are significantly reduced when PTH levels are controlled effectively by the calcimimetic cinacalcet [37, 56]. Given that head-to-head trial data demonstrate etelcalcetide provides more effective control of PTH compared with cinacalcet, it is anticipated that etelcalcetide will also provide a significant reduction in the risk of clinical events.

4.13.5 Conclusions on clinical effectiveness

Etelcalcetide has robustly demonstrated superior SHPT control over placebo and cinacalcet when added to phosphate binder and vitamin D regimens across the broad population of SHPT patients meeting its licensed indication, and in specific subgroups within this, including those with SHPT that is refractory to PB/VD regimens alone. Etelcalcetide is well tolerated with an adverse event profile consistent with the pre-existing comorbid conditions typically associated with SHPT and the mechanism of action of calcimimetics. This favourable benefit:risk profile is maintained with long-term treatment.

This robust supportive evidence base, coupled with its IV administration, which places control of administration in the hands of health care professionals at the end of dialysis, means etelcalcetide represents a significant therapeutic advance in the treatment of SHPT in CKD patients on haemodialysis, that has the potential to address the significant unmet needs for a more effective medical treatment option to which patients with SHPT can be adherent and persistent to ensure they achieve the best possible outcomes. Amgen proposes that etelcalcetide should be recommended as a clinically effective treatment option for patients with SHPT with chronic kidney disease, receiving haemodialysis.

4.14 *Ongoing studies*

The OLE2 open-label extension study (20130213) is ongoing to describe the long-term safety and efficacy of etelcalcetide. Final results are anticipated in 2017.

5 Cost effectiveness

***De novo* cost-effectiveness model**

- The cost-effectiveness of etelcalcetide as a treatment for patients with SHPT undergoing HD was assessed using a *de novo* Markov state-transition model. The model captured the impact of treatment on clinical events (including CV, fracture and death) and was informed by previously published models in this disease area.
- In the base case analysis, etelcalcetide (plus PB/VD) was evaluated in two distinct comparisons: **1)** versus PB/VD alone; **2)** versus cinacalcet (plus PB/VD) in patient's refractory to PB/VD alone. The comparisons presented are aligned with the NICE decision problem and are reflective of clinical practice in the UK.
- Clinical data are predominantly derived from the three pivotal clinical trials for etelcalcetide and the long-term EVOLVE calcimimetic outcome study. For the base case analysis, the effectiveness of etelcalcetide on clinical outcomes was derived by referring to the primary endpoint of the etelcalcetide trials to extrapolate EVOLVE-based HRs; co-variate adjustment was applied to account for imbalances in EVOLVE baseline characteristics and a lag-censored analysis was used to quantify the on-treatment effect.
- Health-state utilities were informed by analysis of the EVOLVE EQ-5D data and therefore reflected HRQoL in the relevant population and for specific events of interest. A GEE regression analysis was used to assess the acute (short-term) and chronic (long-term) impact of major clinical events on HRQoL.
- The economic evaluation underwent extensive validation, including at a UK-specific advisory board featuring nephrologists and health economists who were consulted on key assumptions and parameter inputs.

Base case results

The cost-effectiveness analyses presented in this submission are based on the anticipated list price of etelcalcetide. Amgen has proposed a patient access scheme (PAS) to the Department of Health (DoH) and ICER estimates based on this discounted etelcalcetide price will be presented as an addendum.

- In the base case analysis, etelcalcetide resulted in a QALY improvement of 0.321 versus PB/VD at an increased cost of [redacted] at the NHS list price. This resulted in an ICER of [redacted] per QALY gained.
- For the comparison versus cinacalcet in the refractory population, etelcalcetide resulted in a QALY improvement of 0.069 at an increased cost of [redacted] at the NHS list price, resulting in an ICER of [redacted] per QALY gained.
- One-way sensitivity analyses indicate that the key drivers of the model are relative efficacy for mortality (and to a lesser extent, CV and fracture events) and the dose applied for calcimimetic treatments.

Sensitivity/Scenario analyses

- Probabilistic sensitivity analyses were performed to assess the robustness of the results to plausible variations in the model parameters. The mean ICERs from these analyses were very similar to those in the base case analysis.
- In addition to the probabilistic sensitivity analysis, extensive scenario analyses were conducted. Using ITT-based rather than lag-censored EVOLVE HRs, and using a risk-prediction scheme based on measured biomarkers, the cost, QALY and ICER estimates were broadly consistent with the base case results, demonstrating robustness of the extrapolations of etelcalcetide trial data to long-term clinical outcomes.
- The modelled clinical outcomes are plausible and were validated by clinical experts. The model suggests a reduction in the number of CV and fracture events, as well as improved mortality in the SHPT population. The treatment benefit observed with the addition of etelcalcetide can be explained by the improved biochemical control observed versus PB/VD and cinacalcet, and the impact that this has on clinical outcome events.

Conclusion

- Addition of etelcalcetide to PB/VD has demonstrated superior biochemical control versus both PB/VD alone and cinacalcet plus PB/VD, which translates to improvements in clinical outcomes for patients with SHPT receiving HD.
- The economic evaluation has been developed based on previous models in the disease area. Uncertainty around the extrapolation approaches used and the ultimate ICERs generated have been rigorously investigated through sensitivity and scenario analyses, which confirm the cost-effectiveness results are credible, robust and plausible.

5.1 *Published cost-effectiveness studies*

In accordance with the requirements of the NICE technology appraisal process a systematic literature review (SLR) was conducted to identify relevant cost-effectiveness studies for the treatment of SHPT in adult patients undergoing haemodialysis [74]. The objective of the review was to identify any existing estimates of the cost-effectiveness for SHPT treatments and to inform the development of a *de novo* model in the absence of any previously conducted economic evaluations for etelcalcetide.

Identification of relevant cost-effectiveness studies was a part of a larger review to identify published economic evaluations, studies reporting health-related quality of life or utility data (see Section 5.3.1), and cost and resource studies (see Section 5.4.1). Search strategies followed the recommendations of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook [78].

Electronic databases and resources were initially searched from inception to January 2015 and an update was performed in July 2016. The following specific resources were interrogated:

- Medline (OvidSP): 1946 to 2016/07/wk1
- Medline In-Process Citations (OvidSP): up to 2016/07/18
- Medline Daily Update (OvidSP): up to 2016/07/18
- National Library of Medicine (NLM) PubMed (Internet): up to 2016/07/18
- Embase (OvidSP): 1974-2016/07/18
- NHS Economic Evaluation Database (NHS EED) (Wiley): Cochrane Library 2015/April/Iss2
- EconLit (EBSCO): 1990-2016/07/18
- Cost effectiveness Analysis (CEA) Registry (Internet): www.cearegistry.org: 2003-2016/07/19

The reference lists of retrieved articles and relevant SLRs were also assessed for inclusion in the review as were the studies identified as part of the SLR of clinical effectiveness (described in Section 4.1.2). The full search strategy is presented in Appendix 5.

5.1.1 Inclusion of studies

The PRISMA flow diagram of identified, excluded and included studies is presented in Appendix 6. To be included in the SLR studies had to meet the inclusion criteria outlined in Table 27. The inclusion criteria for health-related quality of life and cost studies are also reported here although the relevant studies identified for these reviews are discussed in Section 5.3.3 and Section 5.4.1, respectively.

Table 27: Inclusion criteria for SLR of economic evaluations

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

Titles and abstracts identified through electronic database and web searching were independently screened by two reviewers. During this initial phase of the screening process any references that did not meet the inclusion criteria were excluded. Full paper copies were obtained for all of the remaining references which were subsequently examined in detail independently by two reviewers to determine whether they met inclusion criteria for the review. All papers excluded at this second stage of the screening process were documented along with the reasons for exclusion (see Appendix 7).

With respect to both screening stages, any discrepancies between reviewers were resolved through consensus by discussion or the intervention of a third reviewer. The trial selection process was detailed in full according to the PRISMA reporting guidelines for systematic reviews (http://www.prisma-statement.org/).

The data extraction process was performed by one reviewer and independently checked for errors against the original trial report by a second reviewer. Any discrepancies were resolved through consensus by discussion or through the intervention of a third reviewer.

5.1.2 Description of identified studies

Sixteen separate cost-effectiveness studies (reported in 17 papers) were identified and have been summarised in Table 28, below.

Of the 16 studies, seven were European, four were from North America, two were from South America and one each were from Asia and Australasia, respectively (Table 28). Three of the four early studies (published in 2007 or before) were designed as decision trees, whereas the other earlier study and all subsequent studies were Markov models (five of which involved microsimulation). All but one of the studies focused on the main population of interest; namely adults with SHPT undergoing haemodialysis. The one exception was the study by Komaba 2012 which provided separate results for two subgroups of patients; those who were eligible for PTx and those who were not. [91]

The most frequently used model structures in the studies where based on combinations of disease control (e.g. PTH control) and key events (e.g. CV, fracture, PTx). Most studies used multiple sources of effectiveness data, although five studies focused almost exclusively on results from an individual trial: OPTIMA in the case of Eandi 2010, Iannazzo 2011, and Iannazzo 2012; ADVANCE in the case of Boer 2012; and EVOLVE in the case of Belozeroff 2015 (Table 28). Nuijten 2015 arbitrarily chose one observational study without any clarity as to the degree of the alignment between the treatments observed in that study and those being compared in the analysis. [92]

The main findings of the identified economic evaluations are reported in Appendix 8.

None of the studies investigated the cost-effectiveness of etelcalcetide for the treatment of SHPT. The study by Garside *et al.* 2007 [75, 93] was the only analysis conducted in the UK and investigated the cost-effectiveness of a cinacalcet-based regimen versus PB/VD over a lifetime horizon. This model was developed by the Peninsula Technology Assessment Group (PenTAG) for the NICE appraisal of cinacalcet (TA117). The authors' main analysis was based on observational studies and expert advice to link PTH levels to event risks. Belozeroff 2015 was the most recent study to investigate the cost-effectiveness of cinacalcet versus PB/VD and the only one to use the EVOLVE clinical trial to directly model event rates. [94]

Although none of the identified studies investigated the cost-effectiveness of etelcalcetide, they were used to inform the development of the *de novo* model presented in Section 5.2. Specifically, the PenTAG and Belozeroff *et al* models were used as key resources as they provided the most relevant analyses to address the decision problem and utilised the best available outcome data for calcimimetics, respectively. Additionally, the economic evaluation by Eandi 2010 *et al.* was also used to explore scenario analyses as the publication presented a risk-prediction equation from which to model clinical outcomes based on reductions in biomarker levels.

5.1.1 Quality assessment

The methodological quality of each individual analysis identified was assessed using the Drummond checklist for cost evaluations. This checklist is widely used throughout the health economics field and incorporates all of the necessary quality assessment criteria specified by the NICE guide to technology appraisals. [74] All quality assessments were performed by two independent reviewers using the relevant checklist items. Any discrepancies in decisions

between the two reviewers were resolved by consensus through discussion or the intervention of a third reviewer. Details of the assessment criteria and results of the quality assessment are provided in Appendix 8.

The quality of economic evaluations identified in the systematic literature review was variable; however, the key studies used to inform the *de novo* model were considered to be of high-quality with a low risk of bias (Appendix 8).

Table 28: Cost effectiveness studies identified

Author, year	Country	Type of model	Time horizon (years or lifetime)	Cost year	Modelled health states/events	Source of effectiveness data
Rosery 2006 [95]	Germany	Decision Tree	1 year	2005	Hospitalised; not hospitalised; death	Two publications by Dobrez 2004 [96] and Teng 2003 [97]
Schumock 2007 [98]	USA	Decision Tree	1 year	2005	Hospitalised; not hospitalised; death	Two observational studies comparing paricalcitol with calcitriol
Garside 2007 [75, 93]	UK	Markov	Lifetime	2005	Dead; controlled PTH; uncontrolled PTH; very uncontrolled PTH; acute states of fracture; CV; parathyroidectomy. States were further defined according to event history i.e. event free; CV event history; fracture history; fracture plus CV history. Adverse drug reaction implies reverting to standard care.	Literature supplemented by expert advice. The authors main analysis is based on event risks derived in Block 2004 [4]. Alternative scenarios based on work of Cunningham [73] as used in the industry submission which was part of the NICE submission.
Narayan 2007 [99]	USA	Decision Tree	2 years	2005	Surgical complication; severe hypocalcaemia; laryngeal nerve injury; bleeding; infection; death; SHPT controlled; SHPT not controlled	All data came from pre-existing literature and trials or from US Renal Data System analysis files
Ray 2008 [100]	USA	Markov	Lifetime	2006	PTH levels ≤300pg/mL; 301-500 pg/mL; 501-800 pg/mL; >800 pg/mL.	When clinical trial data were not available, information was derived from published sources and a large US-based dialysis database was used.
Eandi 2009 [101]	Italy	Markov (micro.)	Lifetime	NR	NR	European multi-centre, open-label study and two reviews
Eandi 2010 [39]	Italy	Markov (micro.)	Lifetime	2009	SHPT; SHPT+PTX; death	OPTIMA trial, various observational studies, National morbidity and mortality registries; presented risk prediction equation
Gordois 2011 [102]	Australia	Markov	10 years	2010	CKD stage 3; CKD stage 4; CKD stage 5; dialysis; CV hospitalization; fracture; death	Set of unspecified trials
Iannazzo 2011 [103]	Spain	Markov (micro.)	Lifetime	2011	SHPT; SHPT+PTX; death	OPTIMA trial, various observational studies, National morbidity and mortality registries

Author, year	Country	Type of model	Time horizon (years or lifetime)	Cost year	Modelled health states/events	Source of effectiveness data
Iannazzo 2012 [104]	Multi-country*	Markov (micro.)	Lifetime	2010	SHPT; SHPT+PTX; death	OPTIMA trial
Boer 2012 [105]	USA	Markov (micro.)	Lifetime	2009	PTH level (300-800;>800pg/mL) with associated Ca and P with rate of fracture; CVD event and PTx (probability unsuitable);death	ADVANCE trial
Komaba 2012 [91]	Japan	Markov	Lifetime	2010	PTH in 4 categories according to 3 thresholds (<180,180-299, 300-499, > 500 pg/ml); death	Trial published by Fukagawa 2008 [106] and assumptions
Menezes 2013 [107]	Brazil	Markov	5 years	NR	NR	Clinical trials or cohort studies
Nishikawa 2013 [108]	Brazil	Markov	10 years	NR	In target according to KDOQI targets (SHPT parameters in target range); patient not controlled (one or more parameters out target range); death.	Set of unspecified trials
Belozeroff 2015 [94]	USA	Markov	Lifetime	2013	Event free; nonfatal CV Event; nonfatal fracture; post-CV event; post fracture; PTx	EVOLVE trial
Nuijten 2015 [92]	Italy	Markov	5 years	2012	CKD stage 5_dialysis; CKD stage 5_transplantation; dead	Single observational study

Ca calcium; CKD chronic kidney disease; CV cardiovascular; CVD cardiovascular disease; EVOLVE Evaluation Of Cinacalcet HCl Therapy to Lower Cardio-Vascular Events; Micro. Microsimulation; KDOQI National Kidney Foundation Kidney Disease Outcomes Quality Initiative; NR not reported; PTH parathyroid hormone; PTx parathyroidectomy; SHPT secondary hyperparathyroidism

*Results are provided for Czech Republic, Italy, Portugal, Spain and Switzerland.

5.2 *De novo analysis*

5.2.1 Patient population

The *de novo* economic analysis considers SHPT patients meeting the licensed indication for etelcalcetide. The model population is therefore aligned with the NICE decision problem (see Section 1.2). The clinical data in the analysis is based on the three pivotal etelcalcetide RCTs, linked to the hard outcomes of the cinacalcet EVOLVE trial.

5.2.1.1 Patient population in etelcalcetide clinical trials

All relevant etelcalcetide trials (Study 20120229, 20120230, 20120360) included adult (≥ 18 years) SHPT patients receiving haemodialysis three times a week for ≥ 3 months (Section 4.5.2). The inclusion criteria regarding PTH at baseline was similar across all trials with PTH >400 pg/mL for the placebo-controlled trials (20120229 and 20120230) and PTH >500 pg/mL for the head-to-head trial (20120360). The studies were conducted globally and the eligibility criteria did not exclude any important segments of the relevant population. [28-30]

All three RCTs utilised in the analysis included similar participants with respect to their mean ages (range of means: 54 to 59 years), gender balance and ethnicity grouping (Table 29). The studies classified, randomised and in some cases analysed patients according to differently defined strata as shown in Table 29. Efficacy results were consistent, irrespective of baseline characteristics and PTH severities, within each of the three trials, and treatment effects of etelcalcetide were comparable across the three trials. [28-30] Further details of the etelcalcetide clinical trials are presented in Section 4.7.

5.2.1.1 Patient population in the EVOLVE clinical trial

The EVOLVE clinical trial was conducted globally and included adult (≥ 18 years) SHPT patients receiving haemodialysis three times a week for ≥ 3 months with baseline PTH inclusion criteria of > 300 pg/mL (3.3.2.1). [37, 56] The eligibility criteria did not exclude any important segments of this the relevant population and the trial population was diverse in terms of age, sex, and race or ethnic group. Further details of the EVOLVE clinical trial are presented in Section 3.3.2.

5.2.1.1 Patient population in the economic model

The etelcalcetide trial populations reflect the anticipated licensed population and the patients in whom etelcalcetide will be used in clinical practice. These are also generally aligned with the EVOLVE trial population that provides hard outcomes data for calcimimetics. As treatment effects in the etelcalcetide trials are consistent, irrespective of baseline demographics and disease severity (see Section 4), the characteristics of the EVOLVE trial population are used in the model for consistency with clinical outcomes. This patient population is defined specifically as adults (aged ≥ 18 years) with chronic kidney disease who have been treated with maintenance haemodialysis 3 times a week for 3 or more months before trial randomisation and who have PTH levels of 300 pg/mL or higher, and an average age of 55 at start.

.

Table 29: Characteristics of participants in the etelcalcetide studies and EVOLVE across treatment groups

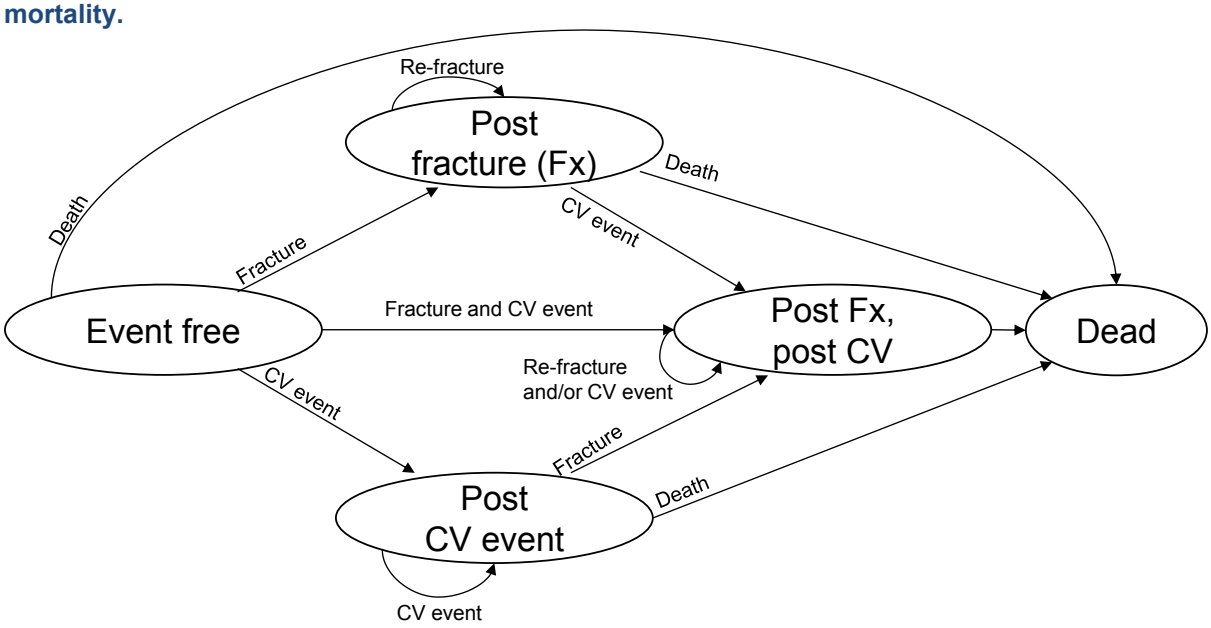
Trial	Amgen 20120229 (n=508)		Amgen 20120230 (n=515)		Amgen 20120360 (n=683)		EVOLVE (n=3883)	
Treatment Arm	**Etelcalcetide (n=254)**	**Placebo (n=254)**	**Etelcalcetide (n=255)**	**Placebo (n=260)**	**Etelcalcetide (n=340)**	**Cinacalcet (n=343)**	**Cinacalcet (n=1948)**	**Placebo (n=1935)**
Mean age (SD) in years	58.4 (SD 14.6)	57.1 (SD 14.5)	58.4 (SD 14.6)	59 (SD 13.9)	54 (SD 13.8)	55.3 (SD 14.4)	54.8 (SD 14.5)	54 (SD 14.2)
Gender (No. of males/females)	151/103	140/114	162/93	165/95	192/148	192/151	1139/809	1166/769
Ethnicity grouping (%)	Asian (2.0%); Black or African American (28.3%); White (68.1%); Other (1.6%)	Asian (1.2%); Black or African American (27.2%); Native Hawaiian or other Pacific Islander (0.8%); White (68.9%); Other (1.6%); Missing (0.4%)	Asian (5.1%); Black or African American (25.1%); Native Hawaiian or other Pacific Islander (2.7%); White (63.9%); Other (2.4%); Missing data (0.8%)	Asian (2.3%); Black or African American (30.8%); Native Hawaiaan or other Pacific Islander (1.2%); White (65.0%); Other (0.8%)	Asian (2.6%); Black (15.9%); Native Hawaiian or Other Pacific Islander (1.8%); White (76.8%); Other (2.9%)	Asian (2.0%); Black (15.2%); Native Hawaiian or Other Pacific Islander (0.9%); White (80.8%); Other (1.2%)	White or Caucasian (57.7%); Black or African American (21.0%); Hispanic or Latino (16.3%); Asian (2.4%); Japanese (0.2%); Alaska Native or Native Hawaiian or other Pacific Islander (0.3%); Aborigine (0.1%); Other (1.5%)	White or Caucasian (57.7%); Black or African American (22.1%); Hispanic or Latino (16.0%); Asian (2.0%); Japanese (0.1%); Alaska Native or Native Hawaiian or other Pacific Islander (0.5%); Aborigine (0.2%); Other (1.1%)
SHPT severity groupings (%)	PTH <600 pg/mL (34.3%); PTH ≥ 600 to ≤ 1000 pg/mL (45.3%); PTH > 1000 pg/mL (20.5%)	PTH <600 pg/mL (33.1%); PTH ≥ 600 to ≤ 1000 pg/mL (44.9%); PTH > 1000 pg/mL (22.0%)	<600 pg/mL (32.9%); ≥ 600 to ≤ 1000 pg/mL (46.3%); > 1000 pg/mL (20.8%)	<600 pg/mL (32.3%); ≥ 600 to ≤ 1000 pg/mL (46.5%); > 1000 pg/mL (21.2%)	PTH <900 pg/mL (49.7%); iPTH ≥900 pg/mL (50.3%)	iiPTH <900 pg/mL (49.9%); iPTH ≥900 pg/mL (50.1%)	iPTH 300 to 600 pg/mL (40.4%); iPTH >600 to 900 pg/mL (23.8%); iPTH >900 to 1200 pg/mL (14.3%); iPTH >1200 pg/mL (21.5%)	iPTH 300 to 600 pg/mL (40.6%); iPTH >600 to 900 pg/mL (24.0%); iPTH >900 to 1200 pg/mL (14.1%); iPTH >1200 pg/mL (21.3%)

PTH, parathyroid hormone; SD, standard deviation

5.2.2 Model structure

The economic analysis is based on a Markov state transition model, implemented in Microsoft Excel 2010. The structure of the model was informed by the cost-effectiveness studies identified in the systematic literature review described in Section 5.1. The decision-analytic model is divided into two separate components which together define the Markov states. The first component describes the health states of adverse clinical outcomes, which include: non-fatal CV events; fractures and all-cause mortality (Figure 13).

Figure 13: Flow diagram of 1st model component: cardiovascular events, fractures and mortality.



All subjects start within the health state 'event free'. This is consistent with a previously published EVOLVE-based cinacalcet cost-effectiveness model [94], which was also used as the main source of the considered incidence rates (Section 5.2.5). In each model cycle, patients can either change health states or remain in the same state. Transition to the non-fatal CV state reflects patients experiencing a non-fatal myocardial infarction, hospitalised unstable angina, heart failure, or peripheral vascular event (as per the definition of CV events in the EVOLVE trial). A fracture event reflects a patient experiencing a non-fatal clinical fracture. The risk of having a subsequent cardiovascular or fracture event is increased after an initial event of that type. Patients may transition to the death health state from any other health state in the model. The probability of death, however, is modelled depending on age, and therefore changes over time. The consequences associated with clinical events are incorporated via utility decrements and event costs, separately by type of event.

In the base case analysis PTx was modelled as an outcome which is aligned with the NICE scope and is consistent with the cinacalcet cost-effectiveness analysis by Belozeroff *et al*. [94]. In the base case analysis, PTx events are linked to corresponding event costs (i.e. surgery and follow-up costs) and short-term health consequences associated with the surgical procedure (i.e. utility decrements); however, the impact of Ptx on long-term clinical outcomes are not captured. This approach was taken due to the paucity of reliable data to both quantify the effect of PTx on clinical outcomes and to inform treatment requirements post-surgery [20]. Nevertheless, the impact of this assumption on the modelled results is evaluated in a scenario analysis (see Section 5.5.5).

The second component of the model describes which treatment patients receive and how this changes over time. All subjects start either on 'calcimimetic treatment' or on 'vitamin D and phosphate binders (PB/VD) only', depending on the treatment arm modelled; the event rates for adverse clinical outcomes (CV events, fractures, death) depends upon the therapy a patient is receiving. Patients can either be persistent with calcimimetic treatment, or discontinue to 'PB/VD only'. In total, the model therefore consists of nine states (four clinical events multiplied with two treatment states plus one state for death).

Consistent with previous calcimimetic cost-effectiveness models and in order to accurately capture the clinical pathways for SHPT, a cycle length of 3 months was applied. [93, 94] Due to the discrete nature of Markov models and in accordance with established modelling guidelines [109], a half-cycle correction was performed. In this model, the 'life-table half-cycle correction' was applied rather than the 'standard half-cycle correction' based on the recommendations of Barendregt and Naimark *et al*. [110, 111].

As the economic evaluation appropriately captures mortality, a life-time horizon was adopted. The life-time horizon was implemented by running the model until the cohort reaches the age 105. Treatment duration is accounted for explicitly as a model input and depends on the persistence assumptions applied for calcimimetic use (see Section 5.2.12). If subjects do not discontinue, the model assumes a life-long calcimimetic treatment.

The analysis was conducted from the perspective of the UK National Health Service (NHS) and both costs and outcomes are discounted at an annual rate of 3.5% (according to the National Institute for Health and Care Excellence (NICE) Methods Guide); this approach is aligned with the NICE reference case. [74]

The key model features are displayed in Table 30.

Table 30: Key features of analysis

Parameter	Value	Justification	Source
Time horizon	Lifetime	Appropriate timescale for evaluating conditions such as SHPT, to enable capturing (differential) lifetime costs and outcomes	NICE guidance [74] Belozeroff et al. 2015 [94]
Cycle length	3 months	To capture the possibility of multiple adverse effects of SHPT such as cardiovascular events and fractures; Consistent with previous economic evaluations in SHPT	PenTAG model [93] Belozeroff et al. 2015 [94]
Half-cycle Correction	Applied	Consistent with previous economic models and the NICE reference case	NICE guidance [74]
Health effects	QALYs	Consistent with previous economic models and the NICE reference case	NICE guidance [74] PenTAG model [93] Belozeroff et al. 2015 [94]
Discounting	Effects: 3.5% Costs: 3.5%	Consistent with previous economic models and the NICE reference case	NICE guidance [74] PenTAG model [93]

Parameter	Value	Justification	Source
Analysis perspective	NHS	Consistent with previous economic models and the NICE reference case	NICE guidance [74] PenTAG model [93]

CV, cardiovascular; NICE; National Institute for Health and Care Excellence, NHS; National Health Service; QALY, quality-adjusted life year, SHPT, secondary hyperparathyroidism

5.2.2.1 Key differences from identified cost-effectiveness studies

The de novo etelcalcetide model is informed by those developed by the Peninsula Technology Assessment Group (PenTAG model) for the NICE appraisal of cinacalcet and the cinacalcet model developed by Belozeroff *et al* [93, 94]. However, a simple adaptation of previous cinacalcet models was not appropriate for several reasons. Importantly, at the time the PenTAG model was developed, clinical outcomes data for cinacalcet from the EVOLVE trial were not yet available. EVOLVE data were not yet available. The *de novo* analysis was therefore developed to utilise the best-available outcomes evidence and was influenced by the Belozeroff *et al* publication in this regard [94].

Furthermore, the *de novo* analysis applies distinct persistence functions to model calcimimetic treatment over time. There are several reasons for taking this approach:

- Calcimimetic efficacy is strongly influenced by adherence and discontinuation. In clinical practice, persistence to cinacalcet is known to be relatively poor. As the model appropriately adopts a lifetime horizon of analysis, it is necessary to account for the fact that a lifetime treatment duration for all patients is potentially an unrealistic reflection of clinical practice;

- Modelling persistence is required in order to link the etelcalcetide clinical trials to the EVOLVE outcomes study given the differences in follow-up time between the trials (26 weeks for etelcalcetide trials vs. 5 years for the EVOLVE trial). The methodology used to link the etelcalcetide trials to EVOLVE outcome data is discussed further in Section 5.2.6.

The assumptions applied when modelling persistence are described in Section 5.2.12.

5.2.3 Intervention technology and comparators

The cost-effectiveness of etelcalcetide is evaluated in two pair-wise comparisons:

- Established clinical practice without calcimimetics; PB/VD in patients with SHPT with chronic kidney disease, receiving haemodialysis (licensed indication)
- Cinacalcet in patients with refractory SHPT

These are in line with the decision problem outlined in the NICE scope (Section 1.2) and the treatment pathway described in Section 3.

For many patients, PTx is not a treatment option (contra-indication and/or preference) and therefore is not considered as a relevant comparator that could be displaced by etelcalcetide (see Section 3). Furthermore, parathyroidectomy is an irreversible procedure that has variable success rate, often leading to severe hypocalcaemia and over-suppression of PTH, and increased healthcare costs post-surgery [20, 21]. The internationally respected KDIGO clinical guidelines [11] recommend parathyroidectomy as an option in patients who are refractory to

medical treatment (including calcimimetic treatment), which would appear to support this approach. For these reasons, and in alignment with the NICE scope and decision problem (Section 1.2), PTx is not a relevant comparator.

5.2.4 Clinical parameters and variables

Clinical data were predominantly derived from the pivotal clinical trials for etelcalcetide and the EVOLVE study. Both published and unpublished data (post-hoc analyses, data on file) from the studies have been used in the analysis. In addition, parameters related to baseline mortality rates were extracted from published literature. All parameters and sources to be discussed in the following sections are summarized in Table 31.

Table 31: Clinical data implemented in the economic model

Aspect	Data	Source
Treatment efficacy	% Patients achieving >30% PTH reduction	Etelcalcetide trials [28-30]
	Hazard ratios of event rates	EVOLVE [37]/Eandi et al. [39]
Baseline clinical event rates	All-cause mortality CV event; initial & subsequent Fracture; initial & subsequent Parathyroidectomy	Boer et al. [105] EVOLVE [37]
Treatment safety	Not included	Not included
Persistence	Persistence of calcimimetics	EVOLVE [37] Reams et al. [19] Urena et al. [112]

CV, cardiovascular; PTH, parathyroid hormone; OLE, open label extension

5.2.5 Treatment efficacy

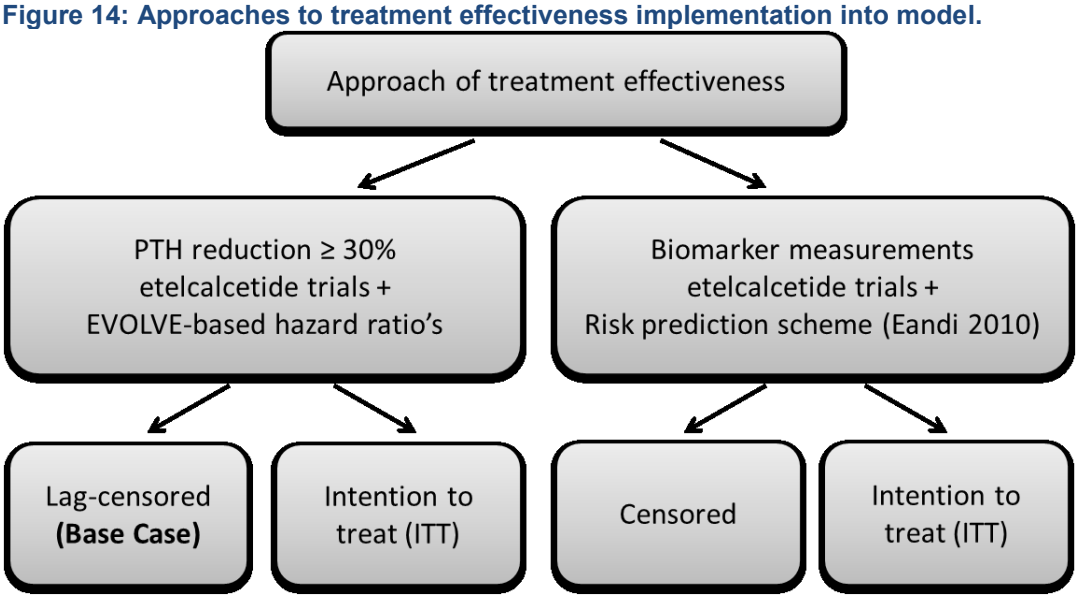
The primary outcome of the etelcalcetide clinical trials was a measure of the ability to lower PTH levels (i.e., the proportion of patients that achieved a 30% reduction or more). However, the model requires treatment effects in terms of clinical outcomes including mortality, CV events and fractures (see Section 5.2.2). Therefore, intermediate outcome measures of the etelcalcetide trials need to be linked to these clinical events. The relationship between PTH (and other biomarker parameters) and clinical events is well established, as is the change in course of SHPT when these parameters are effectively controlled (see Section 3.1.2). The systematic literature review of previous cost-effectiveness analyses demonstrated that various observational data sets have previously been utilised to model clinical outcomes in SHPT (see Section 5.1).

EVOLVE is the only calcimimetic hard outcome trial to directly provide HRs of calcimimetic treatment for mortality, CV, fracture and PTx events. As a robust, long-term RCT (see Section 3.3.2.1), EVOLVE is preferred over observational data sources for modelling calcimimetic efficacy. The risk reduction observed with calcimimetic treatment in the EVOLVE trial to etelcalcetide based on the improved biochemical response of etelcalcetide compared with cinacalcet or placebo in phase 3 trials. However, as discussed in Section 5.2.2, the economic model explicitly distinguishes between persistent and non-persistent subjects to reflect realistic calcimimetic treatment durations and allow the etelcalcetide trials to be linked to EVOLVE data. For the base case analysis, hazard ratios are derived by using the pre-specified lag-censored analysis from EVOLVE, as this assesses the effect-size in an “on-treatment” population (see Section 5.2.6.2).

To explore the validity of the base case approach for extrapolating efficacy to long-term clinical outcomes, two alternative approaches are considered in scenario analyses. First, ITT-based HRs from the EVOLVE trial are used whereby the HRs have been disaggregated to reflect the model structure (see Section 5.2.7). Second, clinical outcomes are modelled based on biomarker data (PTH, calcium and phosphate serum levels) measured within the etelcalcetide trials. A key requirement of this approach is translating the biomarker data into hazard ratios via a risk-prediction scheme. The risk-prediction scheme used in this analysis was based on a published cinacalcet cost-effectiveness model identified in the systematic literature review [39] and was explored with both censored and ITT-based analyses (see Section 5.2.8.)

An overview of the four approaches used to model treatment efficacy is outlined in Figure 14 below.

Figure 14: Approaches to treatment effectiveness implementation into model.



HRs derived from EVOVE are adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin. ITT analyses are disaggregated to reflect the model structure.

The advantages and disadvantages of all four approaches to establishing the efficacy of etelcalcetide based on the extrapolation of PTH and other biomarker measurements is discussed in Section 5.2.9.

5.2.6 Base case efficacy: EVOLVE -based estimates

The base case analysis follows the approach of combining PTH reduction with the hazard ratios from EVOLVE, as explained below.

5.2.6.1 PTH reduction

The primary efficacy endpoint of the etelcalcetide clinical trials was defined as the proportion of patients that achieved at least a 30% reduction in baseline PTH – pooled data across the etelcalcetide clinical trials for the primary endpoint have been presented in Table 32. The relative proportion of patients achieving the primary endpoint can be linked to event-specific hazard ratios from the EVOLVE clinical trial [113].

Table 32: Primary endpoint results (achieving ≥30% reduction of PTH) of the etelcalcetide trials

	Number achieved (n)	Total number (N)	Proportion of patients (%)	Source
Etelcalcetide	612	849	72.1%	Stollenwerk 2016 [113]
Cinacalcet	198	343	57.7%	
Placebo	46	514	8.9%	

5.2.6.2 EVOLVE hazard ratios – cinacalcet vs. placebo

The EVOLVE trial provides the most robust outcomes data for calcimimetics with which to model etelcalcetide and is used to inform the base case analysis. It is the only trial designed specifically to measure hard outcomes with long-term calcimimetic use (see Section 3.3.2) and has been used as the key data source in a previous cost-effectiveness analysis of cinacalcet in SHPT [94]. As discussed in Section 3.3.2.1, the primary unadjusted ITT analysis from EVOLVE showed that patients randomised to cinacalcet experienced numerically fewer composite events, but the risk reduction was not statistically significant (relative hazard 0.93, 95% confidence interval (95% CI) 0.85 to 1.02; p=0.11) [37]. However, as previously discussed, there was a chance imbalance in age between the cinacalcet and placebo arms of the trial, leading to a bias in the ITT analysis. The pre-specified analysis adjusting for baseline characteristics showed a nominally significant hazard ratio for the primary composite end point of 0.88 (95% CI, 0.79 to 0.97; p = 0.008) [37] (see Section 3.3.2). This latter covariate-adjusted analysis has been included in the updated product label for cinacalcet in Europe. [40]

Whereas the covariate-adjusted ITT analysis is suitable to assess *whether* cinacalcet affects the incidence of events, estimates of the treatment effect can differ considerably from the *on-treatment* effect estimates when there is substantial non-adherence in a trial [38]. During the course of the EVOLVE study, a large proportion of patients discontinued randomised treatment [37]. Furthermore, a total of 384 (19.8%) patients randomised to placebo received commercially available cinacalcet and 1207 (62.0%) of patients randomised to cinacalcet discontinued study drug prior to the occurrence of a primary endpoint event, resulting in an effective crossover between study arms. [37]

When combining PTH reduction from the etelcalcetide trials to the hazard ratios from EVOLVE it is necessary to determine the on-treatment effect due to the differences in follow-up durations between the trials (6-months for etelcalcetide trials versus 5-years for EVOLVE). Without adjustment for time-on-treatment, outcomes elicited from EVOLVE would not be consistent with the biomarker-based efficacy data measured in the etelcalcetide trials. In other words, while the covariate-adjusted ITT analysis can account for imbalances in baseline characteristics, it does not take into account the extensive non-adherence observed in EVOLVE and thus would not provide robust outcomes data for etelcalcetide.

The EVOLVE Clinical Trial Investigators anticipated non-adherence during the study period and accounted for this with a pre-specified lag-censored analysis [37, 38]. This approach, along with alternative methods for assessing on-treatment effect (as considered in the NICE DSU Technical Support Document 16), are discussed in more detail below. [114]

Methods to assess on-treatment effect

Several analyses, including methods described in the NICE DSU document, have previously been conducted to account for non-adherence in EVOLVE, including: lag censoring, inverse probability of censoring weights (IPCW), rank preserving structural failure time model (RPSFTM) and iterative parameter estimation (IPE). [38]

These analyses have demonstrated broad consistency when applied to the primary composite endpoint of the EVOLVE trial with HRs ranging from 0.81 to 0.85 (as reported by Kubo *et al.*) [38, 114]. However, as outlined in Section 5.2.2, the model structure requires the treatment effect from EVOLVE to be analysed by type of event – specifically, all-cause mortality, CV events (non-fatal), fractures (non-fatal) and incidence of PTx and the IPCW, RPFSTM, and IPE approaches were associated with a range of methodological challenges and inconsistencies when applied to these specific events. The IPCW method – whereby data for 'switchers' are censored at the point of treatment discontinuation and the remaining observations are weighted with the aim of removing any censoring-related selection bias – was unable to be conducted for the fracture, and PTx endpoints due to the small number of events observed during the trial period. Although both RPFSTM and IPE do not have the same data requirements as IPCW, the parametric accelerated failure time models impose a stronger assumption on the survival time compared to lag-censoring and therefore were not explored for the event-specific treatment effects.

On this basis, the lag-censored analysis was chosen as the most appropriate method to determine on-treatment effects for these specific events. Lag-censored analysis was pre-specified to account for non-adherence in the EVOLVE clinical trial and these data are consistent with published estimates used in a previous economic evaluation [37, 94]. The lag-censoring method is a variation of naïve censoring where data are censored at a specific time point (eg. at the time of non-adherence to treatment) with the aim of establishing the effect attributable to treatment that continues beyond discontinuation. In this analysis, data were censored at 6-months after subjects stopped using the study drug. The lag time of 6-months was specified *a priori* by the EVOLVE Clinical trial Investigators, based on both medical expertise and on previous clinical trials in the disease area [38].

The hazard ratios for the lag-censored covariate-adjusted analysis used in the base case analysis are presented in Table 33 alongside the covariate-adjusted ITT estimates.

Table 33: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo

	Lag-censored HRs[2] [95% CI]	ITT HRs[2] [95% CI]	Source
Cinacalcet vs. placebo			
All-cause mortality	0.80 [0.69, 0.91]	0.87 [0.78, 0.97]	Belozeroff et al 2015 [94]
CV events[1] (non-fatal)	0.78 [0.67, 0.91]	0.85 [0.74, 0.97]	
Fractures (non-fatal)	0.73 [0.59, 0.92]	0.86 [0.72, 1.04]	
PTx (non-fatal)	0.25 [0.19, 0.33]	0.42 [0.34, 0.51]	

CV, cardiovascular; ITT, intention-to-treat; PTx, parathyroidectomy
[1]Myocardial infarction, unstable angina, heart failure and peripheral vascular event
[2]Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

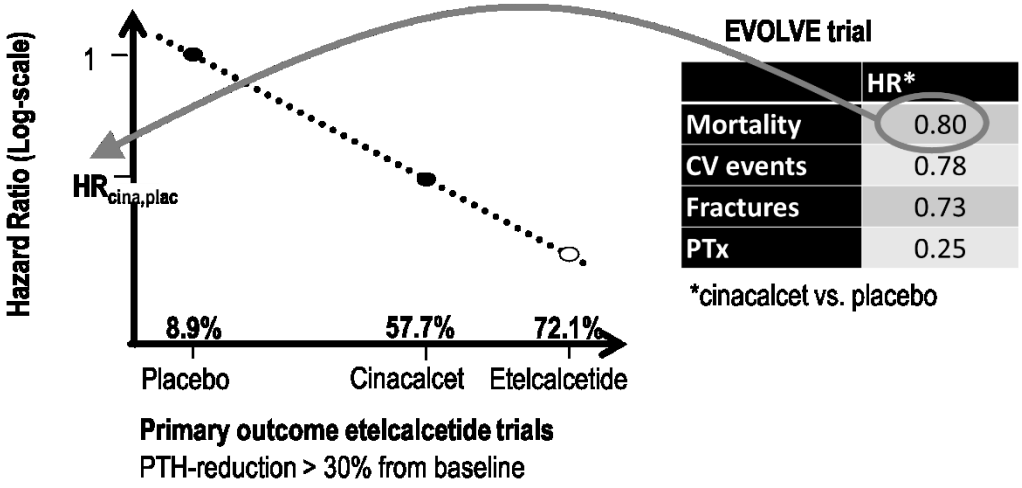
In addition to the alternative ITT-based EVOLVE analyses and the published biomarker approach to extrapolating clinical outcomes, potential uncertainty in the treatment effect estimates derived from EVOLVE were explored extensively in both probabilistic and deterministic sensitivity analyses (see Section 5.5.5).

5.2.6.3 Extrapolation

In order to derive efficacy estimates for etelcalcetide, the hazard ratios of the EVOLVE trial were extrapolated based on the primary endpoint of the etelcalcetide trials. By assuming that the hazard ratio for clinical events with placebo treatment in the EVOLVE trial is 1.0, the hazard

ratios for clinical events with etelcalcetide vs. placebo are derived by linearly extrapolating (on the log scale) the hazard ratios for clinical events with cinacalcet vs. placebo, based on the proportion of patients achieving a greater than 30% reduction in PTH levels with placebo, cinacalcet and etelcalcetide across the 20120229, 20120230 and 20120360 clinical trials. The principle for these calculations is displayed in Figure 15.

Figure 15: Illustration of the EVOLVE-based extrapolation approach to estimate treatment effects of etelcalcetide on clinical outcomes



HR, Hazard ratio; CV, cardiovascular; PTH, parathyroid hormone, PTx, parathyroidectomy

The extrapolation was assumed to be linear on the log-hazard ratio scale to account for the fact that hazard ratios can only take positive values (0 to ∞) [115]. Furthermore, based on the log-transformation the results are not affected by the choice of treatment (placebo or cinacalcet) that serves as a reference point. The resulting HR estimates for etelcalcetide vs. cinacalcet and placebo are presented in Table 34 (for both lag-censored and ITT estimates) and Figure 16 (lag-censored only). To determine 95% CIs, Monte Carlo simulations were implemented via bootstrapping for the primary endpoint of the etelcalcetide trials due to the availability of patient level data [116]. For the hazard ratios, based on the reported confidence intervals, the implementation was based on the log-normal distribution [115].

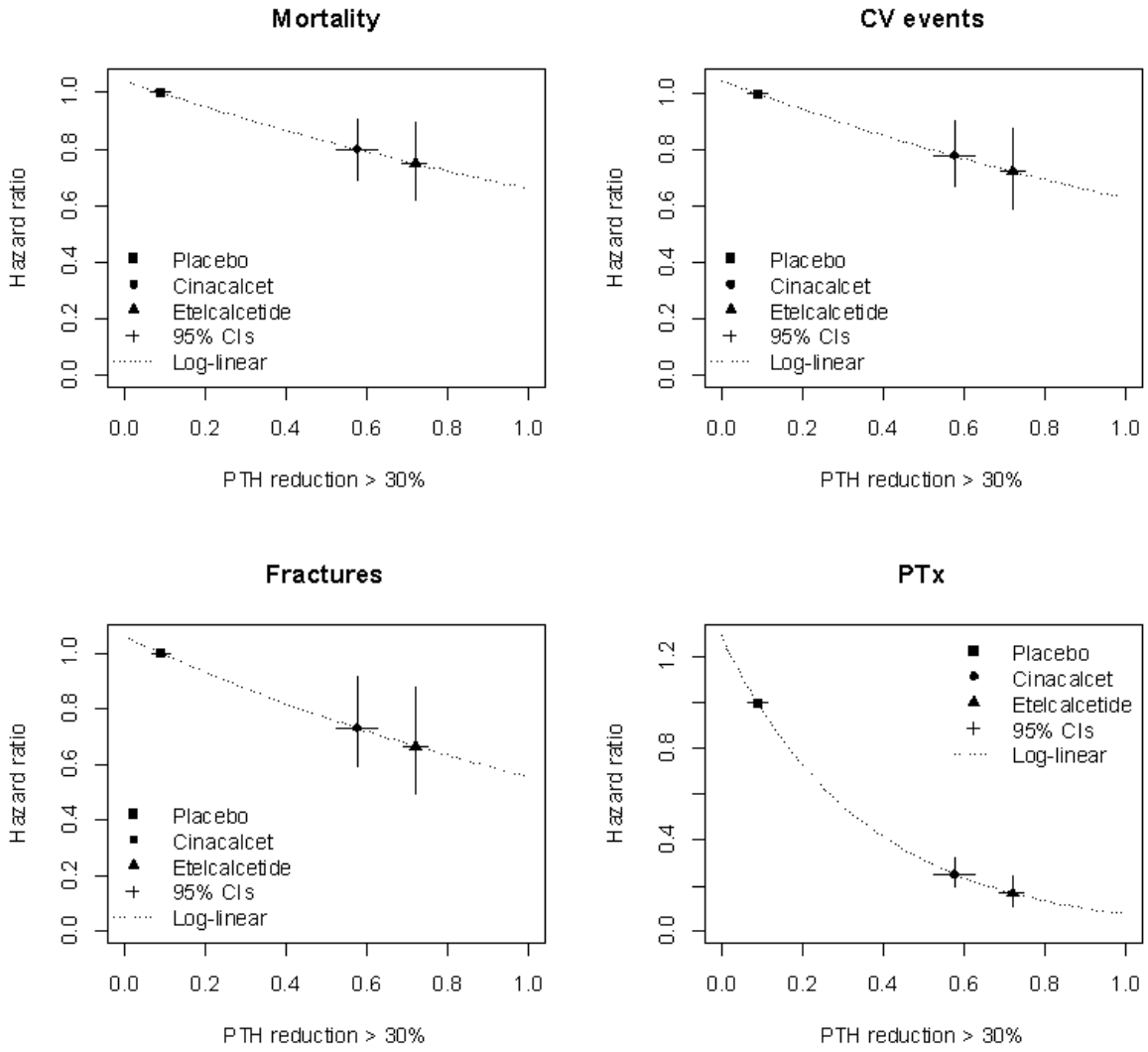
Table 34: Estimated hazard ratios for etelcalcetide based on the EVOLVE trial

	Lag-censored based HRs[3] [95% CI]	ITT based HRs[3] [95% CI]	Source
Etelcalcetide vs. cinacalcet[2]			Stollenwerk 2016 [113]
All-cause mortality	0.94 [0.88, 0.98]	0.96 [0.91, 0.99]	
CV events[1] (non-fatal)	0.93 [0.87, 0.98]	0.96 [0.90, 0.99]	
Fractures (non-fatal)	0.91 [0.83, 0.98]	0.95 [0.89, 1.01]	
PTx (non-fatal)	0.66 [0.51, 0.81]	0.77 [0.65, 0.88]	
Etelcalcetide vs. placebo[2]			
All-cause mortality	0.75 [0.62, 0.89]	0.84 [0.72, 0.96]	
CV events[1] (non-fatal)	0.72 [0.59, 0.88]	0.81 [0.68, 0.96]	
Fractures (non-fatal)	0.67 [0.50, 0.89]	0.82 [0.64, 1.04]	
PTx (non-fatal)	0.17 [0.11, 0.25]	0.33 [0.24, 0.43]	

CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; PTx, parathyroidectomy

[1]Myocardial infarction, unstable angina, heart failure and peripheral vascular event
[2]Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials
[3]Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

Figure 16: Efficacy of etelcalcetide on patient relevant outcomes (extrapolation based on EVOLVE lag-censored covariate-adjusted estimates)



CI, confidence interval; CV, cardiovascular; PTH, parathyroid hormone, PTx, parathyroidectomy

The disaggregation approach used to apply the ITT-based covariate-adjusted HRs in the model as a scenario analysis is discussed in Section 5.2.7 below.

5.2.7 Efficacy: ITT analysis – on-treatment adjustment

As explained in Section 5.2.6, lag-censored efficacy estimates were used as base-case input parameters [38, 94]. To perform scenario analyses using the ITT-based estimates, the treatment effects needed to be disaggregated to account for time spent on- and off-calcimimetic treatment. In order to derive the treatment effect for the duration subjects are persistent, it was assumed that the treatment effect disappears completely after discontinuation. The observed ITT-based hazard ratios were therefore assumed to be a weighted average of the hazard ratios of persistent and non-persistent subjects. Details of the

disaggregation algorithm are provided in Appendix 9. The resulting hazard ratios from this approach, used in this scenario analysis, are presented Table 35.

Table 35: Hazard ratios of treatment persistent patients based on EVOLVE ITT data

	Etelcalcetide vs. cinacalcet: HR [95% CI]	Etelcalcetide vs. placebo HR [95% CI]
All-cause mortality	[redacted]	[redacted]
CV events (non-fatal)	[redacted]	[redacted]
Fractures (non-fatal)	[redacted]	[redacted]
PTx (non-fatal)	[redacted]	[redacted]

CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; PTx, parathyroidectomy

5.2.8 Efficacy: Risk prediction scheme based estimates

In an alternative approach explored in a scenario analysis the event-specific health effects of etelcalcetide were modelled based on biomarker measurements, including PTH, Ca and P. Within the etelcalcetide trials, the biomarkers of each patient were measured every two weeks with the exception of the H2H study where the P levels were measured only every 4 weeks (see Section 4.7). In the analysis, any missing biomarker measurements were interpolated linearly.

The biomarker-based approach requires a risk prediction equation that translates biomarker measurements into event risks (or into risk ratios that can be applied to a baseline risk). Such a risk-prediction equation was used in a previous calcimimetic cost-effectiveness model identified in the systematic literature review (see Section 5.1.2). [39]. The details of the risk equation and how it was applied to the etelcalcetide trial data are provided in Appendix 10.

The point estimates and the confidence intervals for the hazard ratios derived from this approach are reported in Table 36. Estimates for both a censored and ITT analysis of the etelcalcetide trials are presented. In the censored analysis, biomarker measurements were censored post-discontinuation of the investigational product.

The point estimates are similar to those derived from EVOLVE (Table 34); however, the confidence intervals are much wider due to the uncertainty of the risk prediction equation. (Table 36).

Table 36: Estimated hazard ratios based on the risk prediction scheme of Eandi et al.

	Censored HR's[1] [95% CI]	ITT HR's [95% CI]	Source
Etelcalcetide vs. cinacalcet			Stollenwerk 2016 [113]
All-cause mortality	0.94 [0.88, 1.01]	0.94 [0.88, 1.01]	
CV events (non-fatal)	0.99 [0.95, 1.03]	0.99 [0.95, 1.03]	
Fractures (non-fatal)	0.98 [0.76, 1.26]	0.97 [0.74, 1.28]	
PTx (non-fatal)	0.81 [0.63, 1.04]	0.80 [0.62, 1.02]	
Etelcalcetide vs. placebo			
All-cause mortality	0.78 [0.65, 0.93]	0.78 [0.66, 0.93]	
CV events (non-fatal)	0.94 [0.77, 1.15]	0.94 [0.77, 1.14]	
Fractures (non-fatal)	0.86 [0.34, 2.16]	0.86 [0.34, 2.17]	

PTx (non-fatal)	0.37 [0.15, 0.95]	0.38 [0.14, 1.01]	

CV, cardiovascular; HR, hazard ratio; PTx, parathyroidectomy
[1] Subjects were censored at discontinuation of the investigational product

As with the ITT EVOLVE based estimates, the Eandi ITT-based estimates correspond to a mixed population of persistent and non-persistent patients (the analysis included biochemical measurements of all subjects). As such, the treatment effects were disaggregated to account for time spent on- and off- calcimimetic treatment, as outlined in Appendix 9. The resulting values are presented in Table 37.

Table 37: Hazard ratios of treatment persistent patients based on the risk prediction scheme

	Etelcalcetide vs. cinacalcet: HR [95% CI]	**Etelcalcetide vs. placebo HR [95% CI]**
All-cause mortality	[redacted]	[redacted]
CV events (non-fatal)	[redacted]	[redacted]
Fractures (non-fatal)	[redacted]	[redacted]
PTx (non-fatal)	[redacted]	[redacted]

CV, cardiovascular; HR, hazard ratio; PTx, parathyroidectomy

5.2.9 Efficacy: Advantages and disadvantages of extrapolation approaches

The etelcalcetide clinical trials assessed its efficacy using clinically relevant surrogate endpoints rather than hard outcomes. These surrogate endpoint efficacy data therefore require extrapolation to hard outcomes data. The key advantages of the EVOLVE RCT based efficacy extrapolations is that they make use of the most robust calcimimetic long-term outcomes data available to date and the hazard ratios for cinacalcet efficacy directly refer to the effect of cinacalcet treatment on hard outcomes (without relying on extrapolation of surrogate outcomes data). Utilising hard outcomes data for the economic evaluation of etelcalcetide is consistent with the research recommendations made as a result of NICE's previous assessment of cinacalcet in TA117. [15]

However, the extrapolation described in Section 5.2.6.3 relies on two key assumptions. First, on which surrogate endpoint is used for extrapolation, and second, the functional form applied. The rationale for using the PTH reduction of at least 30% from baseline as the surrogate endpoint for extrapolation was that this is the pre-specified primary outcome of the etelcalcetide trials and is regarded by clinicians as clinically meaningful. [25]

Regarding the functional form (i.e. the log-linear relationship between the hazard ratios and the surrogate measure), the goal was to keep the extrapolation approach as simple as possible. Log-transforming hazard ratios, in this context, is a standard approach in biostatistics (e.g. to calculate confidence intervals) in order to guarantee that hazard ratios stay within the valid range. Assuming a linear relationship could in theory have yielded negative hazard ratios; as such, the log-transformation appeared to be necessary to avoid this.

The primary disadvantage of the biomarker-based extrapolation approach is that it does not take into account the direct outcome evidence available from EVOLVE. Furthermore, the identified risk prediction equation from the Eandi *et al.* cost-effectiveness analysis relies on a variety of observational studies to quantify the relationship between biomarkers in SHPT and clinical outcomes. Therefore, it was considered that the approach using the EVOLVE RCT-

based outcomes data would generally be more robust and at lower risk of bias than the approach based on a range of observational studies.

Nevertheless, the biomarker-based approach is explored in a scenario analysis to explore the robustness of extrapolating etelcalcetide data to long-term clinical outcomes. As discussed in Section 5.2.8, two scenarios are considered: ITT-based hazard ratios and hazard ratios that are based on a censoring approach. In the ITT-based analysis, the model assigns the whole treatment effect to the period before subjects discontinue calcimimetic treatment. In reality, and as captured by the lag-censored analysis, the treatment effect fades out over time. The use of ITT-based hazard ratios therefore potentially overestimate the efficacy of etelcalcetide prior to discontinuation. In contrast, the application of censored hazard ratios is consistent with the model structure, but potentially underestimates the value of calcimimetic treatment. Sensitivity analyses using both approaches have therefore been conducted to fully explore the impact of the uncertainty in the biomarker risk-equation approach.

5.2.10 Baseline clinical event rates

5.2.10.1 Baseline mortality

Baseline mortality rates for dialysis patients with SHPT (defined by elevated levels of PTH, Ca and P) were based on published analyses of an administrative database from a large dialysis organisation in the US where 60,000 dialysis patients were followed up for 4 years between 2000 and 2004, i.e. before cinacalcet was made available in the US. [102]

This data source was chosen as the estimates are best aligned with the model assumptions:

- The patient cohort in this database is free from cinacalcet exposure, and therefore corresponds to a PB/VD alone population;
- The size of the population is substantial to provide mortality rates for specific age groups;
- The PTH threshold for inclusion was 300 pg/mL, which corresponds to the target patient population that is modelled.

Mortality rates from the EVOLVE clinical trial were also considered. For consistency, the placebo arm was analysed excluding patients who had received commercial cinacalcet, to reflect the 'PB/VD alone' population. At a starting age of 55 years, as per the base case model, there is limited impact of using either source, but as the EVOLVE data includes a smaller sample size the estimates are less stable at the extremes of age ranges. As such, baseline mortality rates from EVOLVE were considered in a scenario analysis.

Table 38: Baseline mortality rates (events per person year) per age group

Age-group	**Baseline mortality rate**	
Source	Boer et al. [105]	EVOLVE placebo arm; Table 14-4.118.3 [117]
18-34 years	0.045	[redacted]
35-44 years	0.074	[redacted]
45-54 years	0.094	[redacted]
55-64 years	0.126	[redacted]
65-74 years	0.165	[redacted]
75-84 years	0.219	[redacted]
85+ years	0.261	[redacted]

5.2.10.2 Other event rates

The baseline event rates for cardiovascular events, fractures and PTx with PB/VD treatment alone were derived from the EVOLVE trial [94]. Again, the data source was chosen due to its alignment with the assumptions of the decision-analytic model and reflects a population with a PTH level of 300 pg/mL. As the baseline event rates should correspond to a calcimimetic non-exposed population, only data from the placebo arm was taken into account. To align the event rates with the EVOLVE-based efficacy estimates, lag-censored estimates were used. For consistency with the primary composite endpoint, the stroke incidence is excluded from the cardiovascular event incidence in the model.

The baseline event rates with PB/VD alone are displayed in Table 39. In a scenario analysis, the cost and consequences of PTx were fully excluded by setting the event rate for PTx to zero. No increase in mortality after the occurrences of CV events and fractures was taken into account. This assumption was made to avoid double-counting against all-cause mortality which is already captured within the model, as assuming an increased mortality post such events would overestimate the ability of calcimimetics to reduce mortality.

Table 39: Baseline event rates (events per person year) with PB/VD alone

Parameter	Estimate	Standard Error	Source
Non-fatal CV[1]			EVOLVE trial, placebo arm; Lag-censored event rates. Table 14-4.202.791; [118] Table 14-4.212.711 [119]
- first event	[redacted]	[redacted]	
- subsequent event	[redacted]	[redacted]	
Non-fatal bone fracture			
- first event	[redacted]	[redacted]	
- subsequent event	[redacted]	[redacted]	
PTx			
- All events	[redacted]	[redacted]	

CV, cardiovascular; PTx, parathyroidectomy
[1] Myocardial infarction, unstable angina, heart failure and peripheral vascular event

5.2.11 Treatment safety

Overall, etelcalcetide was well tolerated, with an adverse event profile consistent with the pre-existing comorbid conditions typically associated with SHPT in patients with chronic kidney disease on haemodialysis and the mechanism of action of calcimimetics (see Section 4.12). The safety profile of etelcalcetide is also similar to cinacalcet. The patient incidence of decreased blood calcium and symptomatic hypocalcaemia was higher among patients who received etelcalcetide compared with placebo or cinacalcet; however, these events were typically mild or moderate in severity and rarely led to permanent discontinuation of etelcalcetide.

Due to the mild nature and minor differences between treatment groups, no adverse events were included in the model. This is aligned with previous economic analyses conducted in SHPT, including the PenTAG model used to inform NICEs appraisal of cinacalcet in TA117. [15]

5.2.12 Persistence of calcimimetics

As discussed in Section 5.2.2, discontinuation from calcimimetic treatment is captured explicitly as a model input. In the Markov model subjects' transition from 'on-treatment' to

'PB/VD alone'. To specify this input, the model provides several alternative options which combine available data sources with extrapolation assumptions.

5.2.12.1 Discontinuation of cinacalcet

Two main data sources were identified to model persistence with cinacalcet:

- EVOLVE clinical trial [37]
- Real world persistence data from the US based on the publication of Reams et al. [19].

These data sources provide time-to-event discontinuation data which allowed the fitting of a parametric survival curve for extrapolation. For the base-case analysis, the parametric persistence curve derived from EVOLVE is applied to be consistent with the modelled population and efficacy inputs. The EVOLVE trial also had the longest follow-up duration of the identified studies and was based on a large sample size. Real-world persistence data from the US-based study is explored in a scenario analysis. The model inputs and methodologies for both analyses are described in the sub-sections below.

A further scenario analysis was conducted using data from a European based observational study which provided 1-year persistence data for cinacalcet [112]. In this case, to derive persistence data for each point in time, the shape of the discontinuation curve is selected from the parametric discontinuation functions mentioned in the sub-sections below. An overview of 1-year-persistence estimates from all three sources is presented in Table 40 below.

Table 40: One-year calcimimetic persistence based on alternative sources and approaches

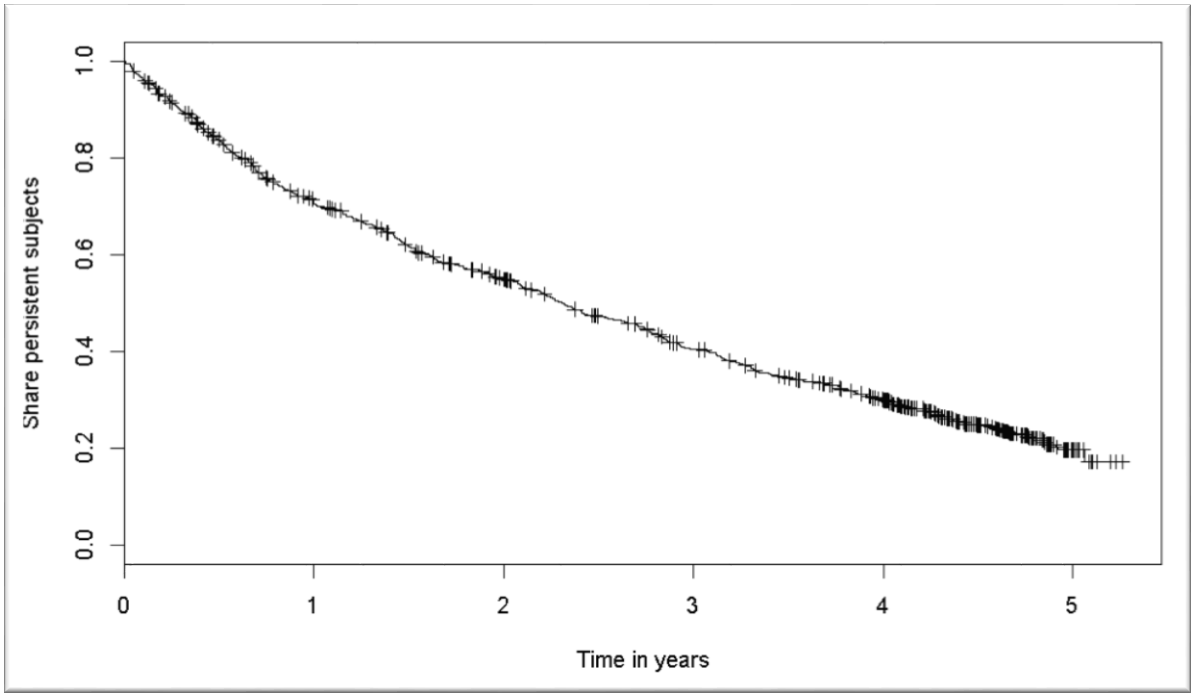
Population	N	1-year persistence	Source
EVOLVE trial population, cinacalcet trial arm	1,938	71% (KM); 72% (parametric)	Amgen data on file; own analyses
US Medicare dialysis patients with prescription drug coverage (Part D); cinacalcet	17,763	27% (as reported); 28% (parametric)	Reams *et al.* 2015 [19]; own analyses
Europe: observational study; cinacalcet	1,865	76%	Urena et al. 2009 [112]

KM, Kaplan-Meier

Persistence based on EVOLVE

A Kaplan-Meier plot of cinacalcet discontinuation, based on the 1938 subjects in the cinacalcet arm of the EVOLVE trial is displayed in Figure 17. To achieve life-time calcimimetic persistence, alternative parametric survival functions have been fitted to these EVOLVE persistence data. According to 'Akaike's information criterion' (AIC) (Weibull: AIC = 7368.8, exponential: AIC = 7369.1, log-normal: AIC = 7443.5, log-logistic: AIC = 7405.6), Weibull gave the best fit (lowest AIC). The regression parameters of the selected parametric function are displayed in Table 41.

Figure 17: Discontinuation from cinacalcet based on EVOLVE.



xxxxxxxTable 41: Regression parameters of EVOLVE cinacalcet discontinuation (parametric distribution, Weibull)

Regression parameters[1]	**Point estimate**	**Standard error**
Intercept	3.654	0.037
Log(scale)	0.045	0.031
Covariance matrix[2]	**Intercept**	**Log(scale)**
Intercept	0.001387	0.000079
Log(scale)	0.000079	0.000938

[1]The regression parameters were derived, based on patient-level data, via the statistical software 'R', package 'survival', function 'survreg'. The time used for regression analysis has been specified in months. The software used for quantification is of relevance, as there are alternative approaches to define the parameters of the Weibull distribution. The parameterization of 'survreg' differs from the parameterization of the R function 'pweibull' as follows: survreg's scale = 1/(rweibull shape); survreg's intercept = log(rweibull scale)

[2]The covariance matrix has been used for probabilistic sensitivity analysis, where alternative parameters are sampled via the Cholesky decomposition method.

United States real world persistence data

The largest sample of real-world cinacalcet persistence is given by Reams et al. [19] in which 17,763 Medicare dialysis patients with prescription drug coverage were followed up to 49 months post treatment initiation. To derive long-term estimates of real-world cinacalcet persistence, parametric discontinuation functions were fitted to the published Reams et al. data. This was done applying the maximum-likelihood approach (see Appendix 11). Based on goodness-of-fit, the Weibull distribution was selected (Weibull: AIC = 42734; log-normal: AIC = 42749; exponential: AIC = 47224, log-logistic: AIC = 42755). The parameters of the fitted function are displayed in Table 42.

Table 42: Regression parameters of the US real-world cinacalcet discontinuation (parametric distribution, Weibull))

Regression parameters[1]	Point estimate	Standard error
Log(shape)	-0.779	0.015
Log(scale)	1.947	0.026
Covariance matrix[2]	**Log(shape)**	**Log(scale)**
Log(shape)	0.000229	-0.000201
Log(scale)	-0.000201	0.000700

[1]The parameter estimates were derived, based on aggregated data, via the maximum likelihood approach applying the statistical software 'R', package 'stats4', function 'mle'. The parametrization corresponds to the R-function 'pweibull'. The time used for the analysis has been specified in months.
[2]The covariance matrix has been used for probabilistic sensitivity analysis, where alternative parameters are sampled via the Cholesky decomposition method.

5.2.12.2 Discontinuation of etelcalcetide

No long-term persistence data are available for etelcalcetide, therefore the relative persistence observed between etelcalcetide and cinacalcet from the phase III head-to-head clinical trial was considered. [30] As summarised in Table 43, there was no significant persistence difference identified between etelcalcetide and cinacalcet (rate ratio based on Cox regression: 1.2 (95% CI 0.82, 1.62).

Table 43: Discontinuation of etelcalcetide and cinacalcet in the head-to-head trial

Study 20120360 [30]	Cinacalcet	Etelcalcetide
Number of subjects	341 (100%)	338 (100%)
Discontinuation within follow-up	59 (17.3%)	67 (19.8%)
Censored[1]	282 (82.7%)	271 (80.2%)
Discontinuation by time [95% CI]		
Week 4	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 20	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Rate ratio of discontinuation based on Cox regression:		
	Hazard ratio	95% CI
Cinacalcet	[redacted]	[redacted]
Etelcalcetide	[redacted]	[redacted]

[1]No discontinuation up to week 26

[redacted] In the absence of a difference in discontinuation between etelcalcetide and cinacalcet in the head-to-head trial setting the base case analysis assumes an equal discontinuation rate for both calcimimetics, with the adopted rate based on cinacalcet discontinuation observed in the EVOLVE trial (as described in Section 5.2.12.1). However, it is plausible that in clinical practice the IV route and HCP-led administration of etelcalcetide could lead to patients being more adherent with etelcalcetide.

5.3 *Measurement and valuation of health effects*

5.3.1 Health-related quality-of-life data from clinical trials

Utility values used for the analysis were taken from the published analysis of HRQoL from the EVOLVE trial. [120] This assessed HRQoL with the EuroQoL (EQ)-5D instrument [121], which measures overall health and health state across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) using a 3-level scale (no problem, some problem and extreme problem). The EQ-5D is a standardised and validated generic instrument, and the preference elicitation is based on a time trade-off algorithm, which is in line with the NICE reference case.

The 5 EQ-5D dimensions were converted into a single utility index using the Dolan algorithm [122]. The algorithm uses time trade-off responses from a representative sample of 2997 non-institutionalized individuals in the UK. The EQ-5D instrument was administered after a study-defined clinical event and at predefined scheduled study visits. The analysis set included patients who had a baseline EQ-5D measurement and at least one measurement post baseline. [120]

5.3.2 Mapping

Mapping was not used within this economic evaluation.

5.3.3 Health-related quality-of-life studies

To inform the utility estimates used in the model a systematic literature review was conducted to health-related quality of life and utilities associated with SHPT. This review was conducted as a part of a broader literature review described previously. The search strategy is described in Section 5.1 and presented in full in Appendix 5.

5.3.3.1 Included studies

The PRISMA flow diagram of identified, excluded and included studies is presented in Appendix 6.To be included in the SLR studies had to meet the eligibility criteria outlined in Section 5.1.1.

Five studies (reported in six papers) providing information about health related quality of life and utilities were identified in the review (Table 44). One study was available as a full paper and an abstract. [58, 123] Three of these measured quality of life in terms of SF-36 scores: a Greek study by Malindretos 2012, a Chinese study by Lun 2014 and a French study by Filipozzi 2015 with completion of self-administered questionnaires for 50, 30 and 124 SHPT patients respectively. [8, 124, 125] Another study from Canada estimated utilities via the Time Trade Off (TTO) method based on evaluations by 199 members of the general population. The most recent study by Briggs 2016 estimated utilities based on the EQ-5D instrument administered to 3,547 SHPT patients in the EVOLVE trial. [120]

Further details of the included studies are reported in Appendix 12.

Table 44: Summary of HRQoL/health state utility studies

First author, year	Country	Study design	HRQoL tool	Type of study population	Number of patients included in study	Mean age (yrs)	SD age (yrs)	% of males
Malindretos 2012 [8]	Greece	Case control (Self-administered questionnaire)	SF-36	SHPT patients	50	62.1	14.9	NR
Davies 2013 [58, 123]	Canada	Preference elicitation using Time Trade Off (TTO) (interview)	TTO	General population	199	46.3	NR	45.2
Lun 2014 [124]	China	Pre-post parathyroidectomy(Self-administered questionnaire)	SF-36	SHPT patients	30	NR	NR	NR
Filipozzi 2015 [125]	France	Prospective cohort (Self-administered questionnaire)	SF-36	SHPT patients	124	67.1	15	58.1
Briggs 2016 [120]	UK	Preference elicitation	EQ-5D	SHPT patients*	3547	54.3	14.3	59.1

NR not reported; SHPT secondary hyperparathyroidism; SD standard deviation; SF-36 Short Form Health Survey – 36 items; yrs years
* EQ-5D values were elicited from SHPT patients and then transformed using utilities elicited from the general population

Two studies estimated utilities, one directly via the TTO method and one using the EQ-5D instrument. [58, 120, 123] The Canadian study by Davies, which elicited utilities directly from the general population using the TTO method, found that secondary hyperparathyroidism resulted in a utility score of 0.6 (SD 0.34), where 1.0 represented “perfect health” (Appendix 12). In this study, utility decrements/increments were also estimated for health states associated with various SHPT associated events (e.g. fractures, kidney transplant, peripheral vascular disease (PVD), myocardial infarction (MI) etc.) Most events were associated with utility decrements, but kidney transplantation and PTx were both associated with utility gains (Appendix 12).

By contrast, the study by Briggs 2016 estimated utilities from the general population, but via the indirect approach. [120] Firstly, from SHPT patients, EQ-5D values were obtained, for which utilities have been elicited from the general population in the UK. The utility of SHPT was estimated to be higher than that by Davies 2013 at 0.71 instead of 0.6. Out of the eight states where Briggs and Davies can be compared, the decrements were larger for Briggs than Davies in six. However, the average age of participants in the SHPT-specific populations were notably different (54.3 years in Briggs 2016 and 46.3 years in Davies 2013) which should be considered when evaluating the results.

The utility values as reported by Briggs 2016 were selected as the most relevant for use in the base case economic evaluation as they were derived from EQ-5D measurements during the EVOLVE clinical trial and were consistent with the model population and key inputs [120]. Furthermore, preferences were elicited from a UK population and the approach is consistent with the NICE reference case. The methodology and inputs used in the model are described further in Section 5.3.5 below.

5.3.4 Adverse reactions

As discussed in Section 5.2.11, adverse reactions to treatments are appropriately not considered in the model.

5.3.5 Health-related quality-of-life data used in cost-effectiveness analysis

Health related quality of life (HRQoL) in this model is captured by utility values which value life-time and produce the health outcome QALYs. Clinical events and symptoms associated with higher PTH levels reduced quality of life in dialysis patients (See Section 3).

A generalised estimating equations (GEE) regression analysis with repeated measures assessed the acute (the first 13 weeks after the event onset) and chronic (all subsequent months post-event) impact of major clinical events on HRQoL [120]. Standard errors were computed using non-parametric bootstrapping [116].

In the utility analysis, separate estimates were produced for the states of ‘myocardial infarction’, ‘hospitalisation for unstable angina’, ‘heart failure’ and ‘peripheral vascular event’. In the economic model, these events are combined into one state ‘cardiovascular event’. To derive the combined estimate for cardiovascular events, the reported incident numbers of events were used for weighting [120] (see Appendix 13). The standard error of the combined estimates was derived via error propagation, assuming Poisson distributed number of events [126]. For consistency with the efficacy inputs of the economic model, stroke was not included in the average utility decrement estimate.

A summary of the utility estimates that have been used in the model are shown in Table 45.

Table 45: Utility estimates used in the decision-analytic model

Utility values	Value	Standard error	Source
Utility dialysis	0.71	0.013	Briggs 2016 [120], (Table 3)
Absolute utility decrements			
CV event months 1-3	0.19	0.014	Briggs 2016 [120] (Table 1; Table 3, error propagation)
CV event after month 3	0.14	0.014	Briggs 2016 [120] (Table 1; Table 3, error propagation)
Fracture months 1-3	0.31	0.023	Briggs 2016 [120] (Table 3)
Fracture after month 3	0.12	0.020	Briggs 2016 [120], (Table 3)
PTx months 1-3	0.06	0.020	Briggs 2016 [120], (Table 3)
PTx after month 3	-	-	Assumption, based on non-significance (p=0.653), [120]
Calcimimetic treatment	-	-	Conservative assumption, as published point estimate implied a slight utility increase [120]

CV, cardiovascular event; PTx, Parathyroidectomy

All clinical events show results in the expected direction (events associated with reduced HRQoL), with many of the coefficients being large in magnitude and highly significant, emphasizing the impact of events on HRQoL. [57] The long-term effect of PTx was associated with a utility gain of 0.01; however, as this was non-significant (p=0.65) a 0-value was applied in the base case analysis.

The original analysis also assessed an effect of cinacalcet treatment on quality of life and demonstrated a significant improvement by a utility increment of 0.02 (p<0.001) [120]. The utility associated with treatment was assumed to be the same for both cinacalcet and etelcalcetide, and was conservatively applied as 0 in the base case analysis; the impact of applying a utility increment was explored in a scenario analysis.

The loss in utility due to a cardiovascular event or fracture was applied in the model by applying the decrements to the baseline utility value. When a patient entered the “post CV, post fracture” state, both utility decrements were deducted. The long-term utility decrements for experiencing cardiovascular events or fractures that resulted in hospitalisation were assumed to apply during the life-time horizon. As in the EVOLVE study, HRQoL was observed for the follow-up time of 5 years and given the life expectancy of the modelled cohort, the actual extrapolation time is limited.

5.3.6 Validation

The validation of the economic evaluation is discussed in more detail in Section 5.9.

5.4 Cost and healthcare resource use identification, measurement and valuation

5.4.1 Resource identification, measurement and valuation studies

To inform the cost and resource estimates used in the model a systematic literature review was conducted. This review was conducted as a part of a broader literature review described previously. The search strategy is described in Section 5.1 and presented in full in Appendix 5.

5.4.1.1 Included studies

The PRISMA flow diagram of identified, excluded and included studies is presented in Appendix 6. To be included in the SLR studies had to meet the eligibility criteria outlined in 5.1.1.

Seven studies (reported in seven papers) provided information on the cost of SHPT as a whole or for different sub-populations (Table 46). Three studies were UK-based (Duenas 2010 [127], Pockett 2012 [128] and Pockett 2014 [129]), three were US-based (Schumock 2011 [98], Lee 2011 [130], and Lee 2013 [10]) and one reported costs for Hungary, Italy, Portugal, Spain and Turkey (Chiroli 2012). Detailed costs reported in the identified studies, presented in Appendix 14, demonstrate that costing processes in one country are likely to be very different from those in other countries and transferability of costings between countries is likely to be fraught with problems. Therefore, only studies conducted in the UK were considered relevant to the decision problem and used to inform the economic analysis.

Populations in the three UK studies were broadly similar in terms of demographics, and all relate to patients undergoing PTx. The studies by Duenas 2010 and Pockett 2012 reported results for a 12 month period whereas Pockett 2014 reported costs for four and 36 month periods taken separately from a database and patient questionnaire. [127-129] The results from Pockett 2014 were used to inform the cost of PTx in the base case analysis. [129]

Table 46: Summary of cost of illness studies

First author, year	Analysis Countries	Cost year	Defining population	Time horizon (mths)	Currency	Number included in study	Mean age (yrs)	SD (yrs)	% of males
Duenas 2010 [127]	UK	NR	Undergoing PTx	12	British Pound (£)	100	49.0	14.0	NR
Schumock 2011 [98]	USA	NR	After PTx	12	US dollar ($)	19	NR	NR	NR
			Before PTx	12	US dollar ($)	2704	52.4	NR	45.2
Lee 2011 [130]	USA	2010	High adherent patient (MPR>=80%)	12	US dollar ($)	1372	63.7	12.8	55.5
			Low adherent patient (MPR<=80%)	12	US dollar ($)	1304	59.9	12.9	52.5
			Non-adherent cinacalcet patients	12	US dollar ($)	2247	61.8	13.8	52.5
Chiroli 2012 [9]	Hungary; Italy; Portugal; Spain; Turkey	2006	Patients with mild SHPT (PTH level of 300-600 pg/ml)	1	Euro (€)	1343	62.0	14.8	57.0
			Patients with severe SHPT (PTH level >800 pg/ml)	1	Euro (€)	472	57.5	15.6	49.0
			SHPT patients	1	Euro (€)	6369	63.0	14.7	57.0
Pockett 2012 [128]	UK	2011	Undergoing PTx	12	British Pound (£)	124	51.1	13.8	NR
Lee 2013 [10]	USA	2011	On dialysis type not reported	1	US dollar ($)	41927	64.4	14.4	57.7
				12	US dollar ($)	41927	64.4	14.4	57.7
				Event Only	US dollar ($)	41927	64.4	14.4	57.7
Pockett 2014 [129]	UK	2010-2011	Undergoing PTx _Costs from database	4	British Pound (£)	124	51.1	13.8	46.8
				36	British Pound (£)	124	51.1	13.8	46.8
			Undergoing PTx _Costs From questionnaire	4	British Pound (£)	79	53.0	6.0	NR
				36	British Pound (£)	79	53.0	6.0	NR

MPR Medication Possession Ratio; PTH parathyroid hormone; PTx parathyroidectomy; SHPT secondary hyperparathyroidism

5.4.1 Intervention and comparators' costs and resource use

Costs used within the model reflect the UK NHS perspective and consist of following components:

- Drug acquisition costs
- Monitoring treatment costs
- Event costs
- Dialysis costs

5.4.1.1 Drug use

The drug consumption of calcimimetics, vitamin D and phosphate binders is based upon the etelcalcetide trials. For this purpose the data from all three pivotal trials (i.e. trials 20120229, 20120230, and 20120360) have been analysed. The drug usage has been quantified based on the "safety analysis set" of the trials. (Safety analysis set: all subjects who received at least one non-missing dose of the investigational product (IP), all subjects who received commercial cinacalcet during the study were excluded). Point estimate of the average doses are calculated as the sum of cumulative doses among all subjects divided by the total IP exposure (days) for all subjects. The standard errors were calculated using the bootstrap method with 10,000 replications [116].

Calcimimetic drug use as assumed in the model is presented in Table 47. The doses are measured based on the EAP of the etelcalcetide trials as these reflect the dosing after an initial titration and are more likely to resemble doses used to control SHPT in clinical practice over the long term. In support of this, the dose of cinacalcet in the head-to-head trial against etelcalcetide is comparable with the cinacalcet dose observed in the EVOLVE trial (5-year follow-up, 66.8 mg/day, Belozeroff et al. 2015 [131]). The doses assumed for etelcalcetide were pooled from the placebo-controlled and head-to-head trials. In a scenario analysis, the average dose observed in the EAP of the head-to-head trial only was considered.

Table 47: Calcimimetic drug consumption during EAP

Drug	Dose (mg/day)[1]	SE	Total exposure (py)	Source
Etelcalcetide: placebo trials	[redacted]	[redacted]	[redacted]	Table 11-6.1.2 [132]
Etelcalcetide: H2H trial	[redacted]	[redacted]	[redacted]	
Weighted average	[redacted]	[redacted]		
Cinacalcet	[redacted]		[redacted]	

EAP, efficacy assessment phase; IP, investigational product; mg, milligram; PY, person years; SE, standard error
[1]Based on the on-treatment population in the etelcalcetide trials

Vitamin D and phosphate binder usage are presented in Table 48. Consistent with the PenTAG model of cinacalcet and PB/VD, no differences in PB/VD usage was modelled between the comparators [93]. The point estimates of PB/VD use were derived by pooling data from all three etelcalcetide trials.

As a summary measure, the overall vitamin D usage is expressed as the "paricalcitol equivalent dose" (1 unit paricalcitol = 0.5 units alfacalcidol = 0.25 units calcitriol = 0.5 units doxercalciferol). This measure has already been used in previous studies, such as the EVOLVE trial and the ADVANCE study [133, 134]. In the case of missing drug prices the drug usage is shifted proportionally to the drugs for which drug prices are available. For vitamin D this shift is based on the paricalcitol equivalent dose [133, 134]. The technical details on how the shifting has been implemented are provided in Appendix 15.

Table 48: Pooled Vitamin D and phosphate binder usage

Drug	Dose		Drug	Dose	
Vitamin D dose	**mcg/day**	**SE**	**Phosphate binder dose**	**g/day**	**SE**
Alfacalcidol (oral)	[redacted]	[redacted]	Aluminium containing	[redacted]	[redacted]
Alfacalcidol (IV)			Calcium containing		
Calcitriol (oral)	[redacted]	[redacted]	Lanthanum carbonate	[redacted]	[redacted]
Calcitriol (IV)	[redacted]	[redacted]	Magnesium containing	[redacted]	[redacted]
Doxercalciferol (oral)	[redacted]	[redacted]	Magnesium & calcium containing	[redacted]	[redacted]
Doxercalciferol (IV)	[redacted]	[redacted]	Sevelamer	[redacted]	[redacted]
Paricalcitol (oral)	[redacted]	[redacted]			
Paricalcitol (IV)	[redacted]	[redacted]			
Total equivalent dose (Paricalcitol)	[redacted]	[redacted]			
Source	Table 11-6.10.2 and Table 11-6.3.13.) [135]				

SE, standard error; IV, intravenous; mcg, microgram; g, gram

5.4.1.2 Drug costs

Drug prices are based on the British National Formulary 2016 [136] and NHS Drug Tariff (April 2016) [137]. Where more than one formulation or pack size was available, market share data from the NHS prescription cost analysis (Prescription Cost Analysis, England - 2015) [138] was used to determine an average cost per unit. Details can be found in Appendix 16.

[redacted] All average drug costs per unit are displayed in Table 49.

Table 49: Average drug cost per unit applied in the analysis

Calcimimetics	**Cost (£/mg)**	**Source**
Cinacalcet	0.145	BNF 62 [136], Prescription Cost Analysis, England, 2015 [138]
Etelcalcetide	[redacted]	Assumption
Vitamin D	**Cost (£/mcg)**	**Source**
Alfacalcidol (oral)	0.223	BNF 62 [136], NHS Drug Tariff (April 2016) [137], Prescription Cost Analysis, England, 2015 [138]
Alfacalcidol (IV)	2.080	
Calcitriol (oral)	0.683	
Calcitriol (IV)	Not available	
Doxercalciferol (oral)	Not available	
Doxercalciferol (IV)	Not available	
Paricalcitol (oral)	2.480	
Paricalcitol (IV)	2.480	
Phosphate binders	**Cost (£/g)**	**Source**

Aluminium containing	0.127	BNF 62 [136], NHS Drug Tariff (April 2016) [137], Prescription Cost Analysis, England, 2015 [138]
Calcium containing	0.103	
Lanthanum carbonate	2.590	
Magnesium containing	0.193	
Magnesium & calcium containing	0.307	
Sevelamer	1.041	

EAP, efficacy assessment phase; IV, intravenous; mcg, microgram; g, gram

The average drug use as presented in Table 47 and Table 48 is multiplied with the average cost as presented in Table 49 to obtain the costs per day.

5.4.2 Event Costs

The costs of cardiovascular events and fractures have been taken from the National Schedule of Reference Costs [139]. The weighted average cost of a cardiovascular-related hospitalization is estimated by taking all (non-)elective and day cases of myocardial infarction, unstable angina, heart failure and peripheral vascular disorders. To estimate the weighted average cost for fracture-related hospitalization, all 'pathological fractures' have been used to calculate a weighted average. In Appendix 17 a detailed overview of these event cost calculations is provided.

The costs related to PTx are taken from a publication identified in the systematic literature review (Section 5.4.1.1) analysing the Proton renal database and routine hospital data in the UK [129]. In this analysis the prices for resource consumption are based on NHS reference costs, the British National Formulary and published literature. Based on 124 patients, the total average costs were £4,932, which have been inflated to 2015 based on the hospital and community health services (HCHS) index. [140] The event costs used for the analysis are displayed in Table 50.

Table 50: Event costs

Parameter	Value	Weight	Source
Myocardial infarction (MI)	£ 2,196	21.6%	National Schedule of Reference Costs 2014-15 [139]
Unstable angina (UA)	£ 1,187	6.6%	
Heart failure (HF)	£ 2,750	31.2%	
Peripheral Vascular Disorders (PVD)	£ 2,342	40.6%	
Weighted average cost CV-related hospitalization	£ 2,362		
Weighted average cost fracture-related hospitalisation	£ 2,669		
Parathyroidectomy	£ 5,108		Pockett et al. [129] HCHS [140]

HCHS, Hospital and community health services

5.4.3 Adverse reaction unit costs and resource use

As discussed in Section 5.2.11, adverse reactions to treatments are appropriately excluded from the model.

5.4.4 Miscellaneous unit costs and resource use

5.4.4.1 Monitoring costs

Consistent with the PenTAG model, monitoring costs are considered in the analysis (Table 51). These costs were applied for all SHPT subjects. In contrast to the PenTAG cinacalcet model [93], for simplicity there is no higher frequency assumed of PTH tests after a PTx event. The costs have been taken from Garside et al. [93] or the National Schedule of Reference Costs, and inflated to 2015 prices where necessary with the HCHS index [140].

Table 51: Monitoring costs

Parameter	Value	Source
Frequency of PTH tests (per quarter)	1	Garside et al. 2007 [93]
Frequency of Calcium tests (per quarter)	3	
Frequency of Phosphate tests (per quarter)	3	
Unit cost of PTH test	£ 24.99	Garside et al. 2007 [93]; HCHS [140]
Unit cost of Calcium test	£ 1.19	National Schedule of Reference Costs 2014-15 [139]
Unit cost of Phosphate test	£ 1.19	

HCHS, Hospital and community health services; PTH, Parathyroid hormone

5.4.4.2 Dialysis costs

Consistent with the independent model of cinacalcet developed by the evidence review group for NICE TA117 [93], and as accepted by NICE in that appraisal, the background cost of dialysis was not included for all patients in the base-case analysis. Therapies that provide valuable life-extending benefit such as etelcalcetide can be perversely penalised due to high dialysis costs which make it very challenging to demonstrate cost-effectiveness [141]. Consequently, the handling of healthcare costs in added years of life due to an intervention is a methodological issue of considerable controversy. In addition, dialysis is a very expensive treatment that has already been accepted as standard for this population, although in itself may not be deemed cost-effective against conventional willingness-to-pay thresholds [93].

A scenario analysis including dialysis costs was performed for completeness only, to demonstrate the issues described above. For this scenario analysis, the frequency of haemodialysis sessions has been taken from the pivotal etelcalcetide trials. The costs of a haemodialysis session has been taken from Garside et al. [93] and inflated to 2015 prices (Table 52). In Appendix 17 a detailed overview of the cost calculations of a haemodialysis session are provided.

Table 52: Dialysis costs

Parameter	Value	Source
Cost of haemodialysis session	£162.24	Garside et al 2007 [93] HCHS [140]
Number of sessions per month	12.8	Etelcalcetide trials, Table 11-6.4 [142]

Cost of dialysis (per month)	£2,076	

5.4.1 Validation

The validation of the economic evaluation is discussed in more detail in Section 5.9.

5.5 Summary of base-case de novo analysis inputs and assumptions

5.5.1 Summary of base-case de novo analysis inputs

A summary of all inputs used in the base case analysis are presented in Table 53.

Table 53: Base case model input parameters

Parameter	Estimate	Standard Error or 95% CI	Source	Section in Submission
Efficacy estimates: etelcalcetide plus vitamin D and phosphate binders vs vitamin D and phosphate binders only				
Hazard ratios (of persistent subjects)			Lag-censored, baseline covariate-adjusted hazard ratios from EVOLVE*	Section 5.2.6
Mortality	0.75	(0.62, 0.89)		
CV events	0.72	(0.59, 0.88)		
Fractures	0.67	(0.50, 0.89)		
PTx	0.17	(0.11, 0.25)		
Efficacy estimates: etelcalcetide vs cinacalcet				
Hazard ratios (of persistent subjects)			Extrapolation of lag-censored, baseline covariate-adjusted hazard ratios from EVOLVE*	Section 5.2.6
Mortality	0.94	(0.88, 0.98)		
CV events	0.93	(0.87, 0.98)		
Fractures	0.91	(0.83, 0.98)		
PTx	0.66	(0.51, 0.81)		
Baseline event rates (events per person year)				
All-cause death			Age-specific mortality rates for dialysis patients with elevated levels of PTH, Ca, and P are from large dialysis organization registries as analysed by Boer 2012.	Section 5.2.10
- 18-34 years old	0.045			
- 35-44 years old	0.074			
- 45-54 years old	0.094			
- 55-64 years old	0.126			
- 65-74 years old	0.165			
- 75-84 years old	0.219			
- 85+ years old	0.261			
Non-fatal CV (excluding stroke)			EVOLVE trial, placebo arm; Lag-censored event rates. Table 14-4.202.791	Section 5.2.10
- first event	[redacted]	[redacted]		

Parameter	Estimate	Standard Error or 95% CI	Source	Section in Submission
- subsequent event	[redacted]	[redacted]	Table 14-4.212.711	
Non-fatal bone fracture				
- first event	[redacted]	[redacted]		
- subsequent event	[redacted]	[redacted]		
PTx	[redacted]	[redacted]		
Utility values				
Utility dialysis	0.71	0.013	Briggs *et al.* 2016 Dolan index	Section 5.3.5
Absolute utility decrements				
Fracture months 1-3	0.31	0.023		
Fracture after month 3	0.12	0.020		
CV event months 1-3	0.19	0.014		
CV event after month 3	0.14	0.014		
PTx months 1-3	0.06	0.020		
Resource usage				
Cinacalcet (mg per day)	[redacted]	[redacted]	Etelcalcetide trial (Study 20120360), EAP	Section 5.4.1
Price cinacalcet (£ per mg)	0.145		BNF	
Parsabiv™ (mg per day)	[redacted]	[redacted]	Pooled analysis of etelcalcetide trials, EAP	
Price Parsabiv™ (£ per mg)	[redacted]		NA	
CV event	£2,362		National Schedule of Reference Costs - Year 2014-15	Section 5.4.2
Fracture	£2,669		National Schedule of Reference Costs - Year 2014-15	
PTx	£5,108		Pockett et al 2014	
Monitoring costs	£32.13 (per quarter)		PenTAG model	

Parameter	Estimate	Standard Error or 95% CI	Source	Section in Submission
Dialysis costs (not considered for the base case analysis)	£2,076 (per month)		National Schedule of Reference Costs - Year 2014-15	Section 5.4.4

CI, confidence interval; CV, cardiovascular; EVOLVE, Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events; GEE, generalized estimating equations; ITT, intent-to-treat;; PenTAG, Peninsula Technology Assessment Group; PTx, parathyroidectomy; USRDS United States Renal Data System
*Lag censored, co-variate adjusted analyses were pre-specified analyses in EVOLVE trial [37]; [113]).

5.5.2 Assumptions

The key model assumptions and their justification are detailed in Table 54 below.

Table 54: Key model assumptions

Assumption	Justification	Section in Submission
Model patient population with PTH >300 pg/mL	Broad PTH >300pg/mL is aligned with EVOLVE enrolment criteria and reflects the population in UK clinical practice with SHPT. It is aligned with the NICE decision problem and anticipated licensed indication.	Section 5.2.1
Hard outcomes data for etelcalcetide and cinacalcet are based on the EVOLVE trial	EVOLVE was designed specifically to determine hard outcomes with long-term calcimimetic treatment; EVOLVE provides the most robust hard outcomes data for calcimimetics based on the well-established inverse relationship between biochemical control and clinical events.	Section 5.2.5
Lag-censored covariate-adjusted hazard ratios were applied as relative treatment effect	Lag-censoring was pre-specified as an alternative method of analysis in EVOLVE, uses data from all randomised patients and preserves their random treatment assignment to determine on-treatment effects that persist after discontinuation (Kubo et al 2015); adjustment for imbalances in baseline characteristics.	Section 5.2.6.2
Log-linear extrapolation of HRs on hard outcomes derived from EVOLVE to etelcalcetide based on the proportion of patients achieving	EVOLVE provides the only trial-based hard outcomes data for long term calcimimetic treatment and so is the preferred source of outcomes data; >30% reduction in PTH reflects the primary endpoint of the etelcalcetide trials, which is the most robust data for etelcalcetide, and is regarded as clinically meaningful by clinicians	Section 5.2.6.3

Assumption	Justification	Section in Submission
>30% reduction in PTH in the etelcalcetide trials		
PTx is an outcome following treatment	EVOLVE trial data already account for effects of PTx on clinical events; robust data on event rates post PTx are lacking; consistent with previously published economic model by Belozeroff et al. 2015	Section 5.2.2
Stroke is not included as an adverse clinical outcome in the model structure	Stroke was neither a primary endpoint in the EVOLVE trial nor did it show statistically significant results; consistent with previously published economic model by Belozeroff et al. 2015	Section 5.2.2
Baseline mortality rate is based on real world data	Real world data (Boer 2012) based on larger sample of patients than EVOLVE and permits age specific mortality rates.	Section 5.2.10.1
No increase in mortality after the occurrences of CV and fracture events	Conservative approach in order to not overestimate the calcimimetic efficacy, as all-cause mortality is modelled separately.	Section 5.2.10.2
Persistence on etelcalcetide is equal to persistence on cinacalcet treatment.	No difference in persistence was observed between etelcalcetide and cinacalcet in the head-to-head study 20120360	Section 5.2.12
EVOLVE trial persistence for cinacalcet, extrapolated via Weibull distribution, is applied for calcimimetic treatment	EVOLVE trial observed persistence is adopted, as it has the longest follow-up, a large sample size, and a 1-year persistence which is relatively close to identified European real-world source of cinacalcet discontinuation rates observed in the study by Urena *et al.* 2009	Section 5.2.12
The long-term utility decrements for experiencing CV events or fractures that resulted in hospitalisation were assumed to apply during the life-time horizon	In the EVOLVE study, HRQoL was observed for the follow up time of 5 years. Given the life expectancy of the modelled cohort, the actual extrapolation time is limited.	Section 5.3.5
Calcimimetic drug use was quantified based on the efficacy assessment phase (EAP) of the etelcalcetide trials	Compared to EVOLVE (5 years of follow-up) the etelcalcetide trial duration (6 months of follow-up) was rather short, in particular taking into account the life-time horizon of the cost-effectiveness model. Therefore, the EAP estimate is more appropriate for long-term extrapolation. Furthermore, the estimate is consistent with cinacalcet drug usage in EVOLVE. However, real-world cinacalcet drug usage has shown to be much lower than trial drug-usage. Applying trial drug usage therefore may overestimate calcimimetic	Section 5.4.1.1

Assumption	Justification	Section in Submission
	costs. Incremental cost-effectiveness ratios based on real world drug usage are expected to be lower.	
PB/VD drug use was assumed equal for all comparators	Alignment with the previous NICE PenTAG model of cinacalcet. Etelcalcetide trials were not powered to detect PB/VD differences among treatments.	Section 5.4.1.1
Dialysis costs are excluded	Dialysis is related to the treatment of the underlying condition of ESRD, rather than to SHPT; dialysis is a very expensive treatment that has already been accepted as standard for this population, although it may not be deemed cost-effective at conventional thresholds; consistent with established economic models, and accepted by NICE in TA117.	Section 5.4.4.2

5.5.3 Probabilistic Sensitivity Analyses

In a probabilistic sensitivity analysis (PSA) alternative input parameters were simultaneously sampled from probability distributions that best reflect the uncertainty of each model input. In the analysis, 1000 simulations were processed to represent the uncertainty of model results by varying all parameters simultaneously by random draws from their assumed distributions [143, 144].

In general, hazard ratios were sampled via the log-normal distribution [115]. However, the model captures the dependency structure between the EVOLVE-based cinacalcet vs. PB/VD hazard ratios, and the extrapolated hazard ratios of etelcalcetide vs. PB/VD. Therefore, the extrapolation approach (Section 5.2.6) was embedded into the Markov model, and the primary outcome of the etelcalcetide trials was sampled via bootstrapping [116]. Baseline event rates, resource usage and costs were sampled via the Gamma distribution which only takes positive values [145]. Utility decrements were sampled based on the normal distribution, whereas absolute utility values (valid range from zero to one) were sampled based on the beta distribution [145]. The persistence function of calcimimetic treatment is based on two correlated regression parameters (Section 5.2.12). Therefore, these two parameters were sampled simultaneously via the Cholesky decomposition method (i.e. assuming a multivariate normal distribution of the regression parameters) [143].

The baseline mortality rates have not been varied probabilistically, because they are based on a large sample of registry data. The stochastic uncertainty of this input has not been reported, but is expected to be small. However, the baseline mortality rates are varied in DSA which confirm this parameter has a relatively limited impact on ICER estimates (see Section 5.7.2).

An overview of all uncertainty distributions is given in Table 55.

Table 55: Summary of uncertainty distributions applied for probabilistic analysis

Variable	Point estimate	Uncertainty measure (e.g. SE or 95% CI)	Distrib.	Source
EVOLVE-based hazard ratios vs. cina /PB/VD	By mortality, CV event, fractures and PTx		Log-normal	Etel trials + EVOLVE [28-30, 37]
Mortality rates	Age-specific	Not varied probabilistically, as based on large registry data; no uncertainty measures reported		Boer et al. 2012 [105]
CV rate (initial)	[redacted]	SE = 0.005	Gamma	EVOLVE [37]
Fracture rate (initial)	[redacted]	SE = 0.003	Gamma	EVOLVE [37]
PTx rate	[redacted]	SE = 0.003	Gamma	EVOLVE [37]
CV rate (recurrent)	[redacted]	SE = 0.024	Gamma	EVOLVE [37]
Fracture rate (recurrent)	[redacted]	SE = 0.047	Gamma	EVOLVE [37]
Utility dialysis	0.71	[0.69, 0.74]	Beta	Briggs et al. [120]
Utility decrements (CV, fracture, PTx)	By type of event, short-term vs. long-term		Normal	Briggs et al. [120]
Calcimimetic persistence	Regression parameters and covariance matrix of parametric distribution		Cholesky decomposition	EVOLVE [37]

		(i.e. multiv. normal)	
Drug usage (calcimimetics, PBs, VDs)	Point estimates and SEs by trial arm	Gamma	Etel trials [28-30]
Monitoring costs	Testing frequency by type of test (PTH, Ca and P)	Gamma	Garside et al. 2007 [93]; NHS 2014/15 [139]
Event costs	By type of event	Gamma	NHS 2014/15 [139]

Cina, cinacalcet; HR, hazard ratio; CV, cardiovascular; Fx, fracture; PTx, parathyroidectomy; PB, phosphate binder; VD, Vitamin D; SE, Standard error; N, number of subjects; M, number of subjects who achieved the outcome; PTH, parathyroid hormone; Ca, calcium; P, phosphorus; CI, confidence interval

[1]No base-case model input, and therefore only varied in scenario analyses

[2]Boostrapping of binary data is implemented via the binomial distribution

Overall parameter uncertainty is illustrated via scatterplots on the cost-effectiveness plane. To assess the probability of etelcalcetide being cost-effective against its comparator at a given willingness-to-pay (WTP) threshold cost-effectiveness acceptability curves (CEACs) are shown [143].

5.5.4 Deterministic Sensitivity Analyses

DSA was conducted univariately. The majority of the parameters were varied within the range of their 95% CIs, which reflect the range of parameter uncertainty (Table 56). Some model inputs, however, were assessed as groups: “PB/VD drug usage”, “Event costs”, “Monitoring costs”, “Utility decrements” and “Age-specific mortality rates”. Grouping was done, as the effect of their single components may be negligible in terms of impact and difficult to interpret. For simplicity, multipliers for these grouped model inputs were implemented. As a DSA range the grouped inputs were simultaneously increased or decreased by 20%. The results of DSA are presented in terms of tables and tornado graphs.

Table 56: Ranges used for deterministic sensitivity analyses

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

Recurrent fracture events	[redacted]	[redacted]	[redacted]	95% CI
Utility dialysis	0.71	0.69	0.74	95% CI
Utility decrements (multiplier)	1	0.8	1.2	Joint assessment
Dose: etelcalcetide	[redacted]	[redacted]	[redacted]	95% CI
Dose: cinacalcet	[redacted]	[redacted]	[redacted]	95% CI
PB/VD drug usage (multiplier)	1	0.8	1.2	Joint assessment
Monitoring costs (multiplier)	1	0.8	1.2	Joint assessment
Event costs (multiplier)	1	0.8	1.2	Joint assessment

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

[1]Exact confidence intervals according to Clopper and Pearson [146]

5.5.5 Scenario Analyses

Several scenario analyses have been conducted to explore the sensitivity of the economic results to key structural and data assumptions used in the model. All scenario analyses are summarised in Table 57.

Table 57: Summary of base case and scenario analyses

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

HR, hazard ratio; ITT, intention to treat; PTx, parathyroidectomy; PB, phosphate binder; VD, Vitamin D; OLE, open label extension

5.6 Base-case results

The primary outcomes of the cost-effectiveness model are the total and incremental costs and QALYs gained. The base case estimates are presented as incremental costs per QALY gained over a life time horizon, discounted to net present values. Additionally, total number of life years, CV related events, bone fractures and parathyroidectomy are presented.

Four types of analyses are shown: a deterministic base case analysis, and three types of sensitivity analysis. These are multivariate probabilistic sensitivity analysis, deterministic univariate sensitivity analyses and scenario analyses.

5.6.1 Base-case cost effectiveness analysis results

Aligned with the decision problem outlined in Section 1.2 the base case cost-effectiveness results are presented in the broad licensed indication comparing etelcalcetide (plus PB/VD) with PB/VD regimens alone and in patients with refractory SHPT comparing etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD). As these are distinct populations, pairwise analysis, rather than a fully incremental analysis, is appropriate.

5.6.1.1 Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD

The incremental cost per life year at the anticipated list price of etelcalcetide is presented for etelcalcetide (plus PB/VD) vs. PB/VD in Table 58 below. The discounted life-year gain of 0.483 translates to a discounted QALY benefit of 0.321 and results in an ICER of £45,983 per QALY (Table 59).

Table 58: Incremental cost per life year (discounted) – based on anticipated list price

	Total Cost	Δ Cost	Total LYs	Δ LYs	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	6.423	-	-
PB/VD only	[redacted]	[redacted]	5.985	0.438	[redacted]

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

Table 59: Incremental cost per QALY (discounted) – based on anticipated list price

	Total Cost	Δ Cost	Total QALYs	Δ QALYs	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	4.109	-	-
PB/VD	[redacted]	[redacted]	3.788	0.321	[redacted]

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

5.6.1.2 Refractory SHPT – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

The incremental cost per life year at the anticipated list price of etelcalcetide is presented for etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) in Table 60 below. The discounted life-year gain of 0.094 translates to a discounted QALY benefit of 0.069 and results in an ICER of £101,839 per QALY (Table 61).

Table 60: Incremental cost per life year (discounted) – based on anticipated list price

	Total Cost	Δ Cost	Total LYs	Δ LYs	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	6.423	-	-
Cinacalcet*	[redacted]	[redacted]	6.329	0.094	[redacted]

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

Table 61: Incremental cost per QALY (discounted) – based on anticipated list price

	Total Cost	Δ Cost	Total QALYs	Δ QALYs	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	4.109	-	-
Cinacalcet*	[redacted]	[redacted]	4.040	0.069	[redacted]

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

5.6.2 Clinical outcomes from the model

The model estimates of the total number of events (CV, fracture, PTx and death) per 100 patient-years are shown per comparator in Table 62 below. In line with the hazard ratios presented, the lowest number of events is associated with etelcalcetide (plus PB/VD) and the highest with PB/VD alone. The clinical outcome results of the model underwent extensive face-validity assessments and were considered to be clinically valid (see Section 0).

Table 62: Cumulative number of events per 100 patient-years per comparator

	Etelcalcetide*	Cinacalcet*	PB/VD
CV events	27.1	27.7	29.9
Fractures	5.3	5.5	6.0
PTx	3.5	3.7	4.9

PTx, parathyroidectomy; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

5.6.3 Disaggregated results of the base case incremental cost effectiveness analysis

5.6.3.1 Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD

The accrued (un)discounted life years and QALYs during the entire life-time horizon are summarised in Table 63 and Table 64. In line with the hazard ratios for all-cause mortality, etelcalcetide (plus PB/VD) results in an increase in the accrued life years vs. PB/VD alone.

Table 63: Summary of total life years gained – etelcalcetide (plus PB/VD) vs. PB/VD

	Etelcalcetide*	PB/VD	Increment
Undiscounted life years	7.895	7.319	0.576
Discounted life years	6.423	5.985	0.438

PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

The higher total QALYs gained by etelcalcetide are as a result of the lower clinical event rates in this arm and the reduction in PTx (Table 64). A greater amount of time is spent in the 'event-free' health state with less time in the clinical events states, leading to less utility decrements. The majority of the QALY gains are due to the decrease in mortality rate and subsequent additional life years gained.

Table 64: Summary of total QALYs gained: etelcalcetide (plus PB/VD) vs. PB/VD

Health state	QALY Etelcalcetide*	QALY PB/VD	Increment	Absolute increment	Percentage of total QALY gain, %%
Event free	2.665	2.338	0.328	0.328	89.6%
Post CV	0.856	0.842	0.015	0.015	4.0%
Post fracture	0.314	0.318	-0.004	0.004	1.2%

Post CV & fracture	0.275	0.293	-0.018	0.018	5.0%
PTx decrement	-0.002	-0.003	0.001	0.001	0.2%
Total	**4.109**	**3.788**	**0.321**	**0.365**	**100.0%**

PTx, parathyroidectomy; CV, cardiovascular; QALY, quality-adjusted life-year; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

The accrued discounted costs during the life-time horizon are summarised in Table 65. PB/VD alone is associated with lower costs as calcimimetic treatment costs (which account for the majority [redacted] of the total cost increment) are not included in this arm. Additional cost increments for the etelcalcetide treatment arm are due to the life year gains, and cost-offsets are observed due to a reduction in clinical outcomes and PTx.

Table 65: Summary of total costs: etelcalcetide (plus PB/VD) vs. PB/VD – based on anticipated list price

Item	Cost Etelcalcetide*	Cost PB/VD	Increment	Absolute increment	Percentage of total cost increment
Calcimimetics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phosphate binders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fractures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PTx, parathyroidectomy; CV, cardiovascular; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

5.6.3.1 Refractory SHPT – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

The accrued (un)discounted life years and QALYs during the entire life-time horizon are summarised in Table 63 and Table 64 for etelcalcetide (plus PB/VD) and cinacalcet (plus PB/VD). The etelcalcetide treatment arm is associated with an increase in life year gains which reflect the hazard ratios for all-cause mortality described previously.

Table 66: Summary of total life years gained – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

	Etelcalcetide*	Cinacalcet*	Increment
Undiscounted life years	7.895	7.771	0.124
Discounted life years	6.423	6.329	0.094

PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

The higher total QALYs gained by etelcalcetide are as a result of the lower clinical event rates in this arm and the reduction in PTx (Table 64). A greater amount of time is spent in the 'event-free' health state with less time in the clinical events states, leading to less utility decrements.

As with the comparison vs. PB/VD alone, the majority of the QALY gains are due to the decrease in mortality rate and subsequent additional life years gained.

Table 67: Summary of total QALYs gained: etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

Health state	QALY Etelcalcetide*	QALY Cinacalcet*	Increment	Absolute increment	Percentage of total QALY gain, %%
Event free	2.665	2.593	0.072	0.072	91.4%
Post CV	0.856	0.855	0.002	0.002	2.0%
Post fracture	0.314	0.316	-0.001	0.001	1.7%
Post CV & fracture	0.275	0.279	-0.004	0.004	4.8%
PTx decrement	-0.002	-0.002	0.000	0.000	0.1%
Total	**4.109**	**4.040**	**0.069**	**0.079**	**100%**

PTx, parathyroidectomy; CV, cardiovascular; QALY, quality-adjusted life-year; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

The accrued discounted costs during the life-time horizon are summarised in Table 65. The total costs are higher for etelcalcetide compared to cinacalcet and PB/VD, due to increases in calcimimetic drug cost and slightly due to the increased life years in the etelcalcetide arm leading to more drug and monitoring costs. Cost-offsets are observed due to reduction in clinical outcomes.

Table 68: Summary of total costs: etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – based on anticipated list price

Item	Cost Etelcalcetide*	Cost Cinacalcet*	Increment	Absolute increment	Percentage of total cost increment
Calcimimetics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phosphate binders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fractures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PTx, parathyroidectomy; CV, cardiovascular; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

5.7 *Sensitivity analyses*

5.7.1 Probabilistic sensitivity analysis

5.7.1.1 Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD

The scatter plot of incremental QALYs and costs and the cost-effectiveness acceptability curve of etelcalcetide (plus PB/VD) vs. PB/VD alone are presented in [redacted] and [redacted] below.

Figure 18: Scatter plot of incremental QALYs vs. incremental costs of etelcalcetide (plus PBVD) vs. PB/VD – based on anticipated list price

Figure 19: Cost-effectiveness acceptability curve for etelcalcetide (plus PB/VD) vs. PB/VD – based on anticipated list price

The table below presents the mean outputs resulting from the simulations of the PSA. The results are highly consistent with the deterministic outputs.

Table 69: Mean probabilistic results (discounted) – based on anticipated list price

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	4.115 (0.123)	-	-

PB/VD only	[redacted]	[redacted]	3.791 (0.087)	0.324 (0.083)	[redacted]

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

5.7.1.1 Refractory SHPT – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

The scatter plot of incremental QALYs and costs and the cost-effectiveness acceptability curve of etelcalcetide vs. cinacalcet are presented in Figure 20 and Figure 21 below.

Figure 20: Scatter plot of incremental QALYs vs. incremental costs of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – based on anticipated list price

[redacted]

Figure 21: Cost-effectiveness acceptability curve for etelcalcetide vs. cinacalcet – based on anticipated list price

[redacted]

The table below presents the mean outputs resulting from the simulations of the PSA. The results are highly similar to the deterministic outputs.

Table 70: Mean probabilistic results (discounted) – based on anticipated list price

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Etelcalcetide*	[redacted]	[redacted]	4.115 (0.123)	-	-
Cinacalcet*	[redacted]	[redacted]	4.046 (0.111)	0.069 (0.024)	[redacted]

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

5.7.2 Deterministic sensitivity analysis

5.7.2.1 Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD

Deterministic sensitivity analyses for etelcalcetide (plus PB/VD) vs. PB/VD are displayed in Table 71 and Figure 22. The tornado diagram presenting the uncertainty in the ICER for the model parameters shows that the results are most sensitive to the relative efficacy of etelcalcetide (plus PB/VD) vs. PB/VD alone upon mortality and to a lesser extent, upon CV and fracture events. Furthermore, the assumed dose of etelcalcetide is influential as it determines the additional drug costs compared to PB/VD alone. Other parameters have limited impact on the results.

Table 71: Summary of univariate sensitivity analyses of etelcalcetide (plus PB/VD) vs. PB/VD

Parameter	ICER low Input	ICER high Input
HR mort. (vs. PB/VD)	[redacted]	[redacted]
HR CV (vs. PB/VD)	[redacted]	[redacted]
HR Fx (vs. PB/VD)	[redacted]	[redacted]
HR PTx (vs. PB/VD)	[redacted]	[redacted]
Mortality rate	[redacted]	[redacted]
CV rate	[redacted]	[redacted]
Fracture rate	[redacted]	[redacted]
PTx rate	[redacted]	[redacted]
Utility dialysis	[redacted]	[redacted]
Utility decrements	[redacted]	[redacted]
Vitamin D + PB usage	[redacted]	[redacted]
Etelcalcetide dose	[redacted]	[redacted]
Event costs	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
Rate further CV event	[redacted]	[redacted]
Rate re-fracture	[redacted]	[redacted]
Persistence	[redacted]	[redacted]

CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RR, relative risk; PB, phosphate binder; PTx, parathyroidectomy; VD, vitamin D.

Figure 22: Tornado diagram on the ICER for etelcalcetide (plus PB/VD) vs. PB/VD

[redacted]

5.7.2.1 Refractory SHPT – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

Deterministic sensitivity analyses of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) are displayed in Table 72 and Figure 23. The tornado diagram presenting the uncertainty in the ICER for the model parameters shows that the results are most sensitive to the relative efficacy of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) upon mortality and, to a much lesser extent, upon CV and fracture events. The assumed doses of calcimimetics are also influential, as they determine the major cost component of drug costs. Other parameters have limited impact on the results.

Table 72: Summary of univariate sensitivity analyses of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

Parameter	ICER low Input	ICER high Input
HR mort. (vs. cina)	[redacted]	[redacted]
HR CV (vs. cina)	[redacted]	[redacted]
HR Fx (vs. cina)	[redacted]	[redacted]
HR PTx (vs. cina)	[redacted]	[redacted]
Mortality rate	[redacted]	[redacted]
CV rate	[redacted]	[redacted]
Fracture rate	[redacted]	[redacted]
PTx rate	[redacted]	[redacted]
Utility dialysis	[redacted]	[redacted]
Utility decrements	[redacted]	[redacted]
Vitamin D + PB usage	[redacted]	[redacted]
Etelcalcetide dose	[redacted]	[redacted]
Cinacalcet dose	[redacted]	[redacted]
Event costs	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
Rate further CV event	[redacted]	[redacted]
Rate re-fracture	[redacted]	[redacted]
Persistence	[redacted]	[redacted]

CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RR, relative risk; PB, phosphate binder; PTx, parathyroidectomy; VD, vitamin D.

Figure 23: Tornado diagram on the ICER for etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)


[redacted]
ry

5.7.3 Scenario analysis

As discussed in Section 5.2.5, several scenario analyses were conducted to explore the uncertainty around the EVOLVE lag-censored efficacy estimates in the model. The results of these analyses are discussed specifically for each pair-wise comparison in the sub-sections below. A discussion of all other scenarios, as outlined in Table 57, is also provided.

5.7.3.1 Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD

Efficacy-based scenario analyses

The results of the three efficacy-based scenario analyses are presented in Table 74 below. The co-variate adjusted ITT–based analysis of the EVOLVE trial data yield comparable incremental cost, QALY and resulting ICER estimates to the base case analysis for the comparison of etelcalcetide (plus PB/VD) vs. PB/VD. However, as anticipated, this analysis leads to a slight reduction in the ICER compared to the base case estimate; this is because the scenario has the potential to overestimate the efficacy of etelcalcetide as the whole treatment effect is assigned to the period prior to discontinuation. In reality, and as captured by the lag-censored analysis, the treatment effect fades out over time.

The application of the external risk prediction scheme from Eandi *et al* to model hard outcomes also produces results that are broadly similar to the base case analysis. In particular, the incremental costs are highly consistent. This approach does however lead to an increase in the ICER compared to the base case analysis, mostly due to the differences in the hazard ratio for mortality, which results in a lower incremental QALY benefit for etelcalcetide. The censored analysis is regarded as an extreme case as the treatment benefit of etelcalcetide is likely to be underestimated. Furthermore, as the Eandi *et al* risk prediction equation is based on multiple observational studies, there is likely to be an increased risk of bias in the approach.

Table 73: Etelcalcetide (plus PB/VD) versus PB/VD alone – results of efficacy based scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.321	[redacted]
Efficacy: EVOLVE ITT disaggregated	[redacted]	0.346	[redacted]
Efficacy: Eandi; censored	[redacted]	0.247	[redacted]
Efficacy: Eandi; ITT disaggregated	[redacted]	0.292	[redacted]

As discussed in Section 5.2.9, the lag-censored analysis is considered to be the most appropriate method for modelling the impact of etelcalcetide treatment on clinical outcomes. Nevertheless, the scenario analyses presented above demonstrates that the efficacy of etelcalcetide is robust when extrapolating to clinical outcomes considering the likely bias in each approach.

Other Scenario analyses

The results of the additional scenario analyses described in Section 5.5.5 are presented in Table 74 for the comparison of etelcalcetide (plus PB/VD) vs. PB/VD alone. The majority of the analyses presented are highly aligned with the base case estimates demonstrating that varying the input parameters have limited effect on the results.

Inclusion of dialysis costs substantially increase the ICER as etelcalcetide increases the life-expectancy of the modelled cohort and accrues the high ongoing costs of renal replacement therapy. The handling of healthcare costs in added years of life due to an intervention is a methodological issue of considerable controversy. 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 at conventional willingness to pay thresholds [93].

Alternatively, including the measured impact of calcimimetic treatment on utility values improves the results of etelcalcetide (plus PB/VD) as the incremental QALYs are increased.

Table 74: Etelcalcetide versus PB/VD alone – results of scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.321	[redacted]
Age at baseline: 45 years	[redacted]	0.317	[redacted]
Age at baseline: 65 years	[redacted]	0.316	[redacted]
PTx: not included (rate=0)	[redacted]	0.320	[redacted]
Mortality: EVOLVE	[redacted]	0.310	[redacted]
Discontinuation: Reams et al	[redacted]	0.145	[redacted]
Discontinuation: Urena et al.	[redacted]	0.358	[redacted]
Utility: Impact calcimimetic treatment	[redacted]	0.366	[redacted]
Calcimimetic drug use: EAP; head to head	[redacted]	0.321	[redacted]
Dialysis costs: included	[redacted]	0.321	[redacted]
Discount rate: 0%	[redacted]	0.412	[redacted]
Discount rate: 6%	[redacted]	0.274	[redacted]

5.7.3.2 Refractory SHPT – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

Efficacy-based scenario analyses

The results of the three efficacy-based scenario analyses are presented in Table 74 below. The co-variate adjusted ITT–based analysis of the EVOLVE trial data yield comparable incremental cost, QALY and resulting ICER estimates to the base case analysis for the comparison of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD). This analysis leads to a slight reduction in the ICER compared to the base case estimate; this is because the scenario has the potential to overestimate the efficacy of etelcalcetide as the whole treatment effect is assigned to the period prior to discontinuation. In reality, and as captured by the lag-censored analysis, the treatment effect fades out over time.

The application of the external risk prediction scheme from Eandi *et al.* to model hard outcomes also produces results that are broadly similar to the base case analysis. In all cases, both the incremental costs and incremental QALYs are consistent; the differences observed in the ICER estimates are largely due small differences in observed in the denominator of this ratio (QALY). This approach results in ICERs either side of the base case estimates depending

on whether the ITT-based or censoring analysis is used. As with the comparison vs. PB/VD alone, the censored analysis potentially underestimates the treatment benefit of etelcalcetide resulting in reduced QALY gains and an increased ICER. Although the lag-censored analysis is considered to be the most appropriate method for modelling the impact of etelcalcetide treatment on clinical outcomes, the scenario analyses presented below demonstrate that the efficacy of etelcalcetide is robust when extrapolating to clinical outcomes considering the likely bias in each approach.

Table 75: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of efficacy-based scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.069	[redacted]
Efficacy: EVOLVE ITT disaggregated	[redacted]	0.074	[redacted]
Efficacy: Eandi; censored	[redacted]	0.057	[redacted]
Efficacy: Eandi; ITT disaggregated	[redacted]	0.074	[redacted]

Other Scenario analyses

The results of the additional scenario analyses described in Section 5.5.5 are presented in Table 74 for the comparison of etelcalcetide (plus PB/VD) vs. PB/VD alone. The majority of the analyses presented are highly aligned with the base case estimates demonstrating that varying the input parameters have limited effect on the results.

Inclusion of dialysis costs substantially increase the ICER as etelcalcetide increases the life-expectancy of the modelled cohort and accrues the high ongoing costs of renal replacement therapy. The handling of healthcare costs in added years of life due to an intervention is a methodological issue of considerable controversy. 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 at conventional willingness to pay thresholds [93].

Alternatively, including the measured impact of calcimimetic treatment on utility values improves the results of etelcalcetide (plus PB/VD) as the incremental QALYs are increased.

Table 76: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.069	[redacted]
Age at baseline: 45 years	[redacted]	0.067	[redacted]
Age at baseline: 65 years	[redacted]	0.069	[redacted]
PTx: not included (rate=0)	[redacted]	0.069	[redacted]
Mortality: EVOLVE	[redacted]	0.067	[redacted]
Discontinuation: Reams et al	[redacted]	0.031	[redacted]
Discontinuation: Urena et al.	[redacted]	0.078	[redacted]
Utility: Impact calcimimetic treatment	[redacted]	0.070	[redacted]
Calcimimetic drug use: EAP; head to head	[redacted]	0.069	[redacted]
Dialysis costs: included	[redacted]	0.069	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER
Discount rate: 0%	[redacted]	0.089	[redacted]
Discount rate: 6%	[redacted]	0.059	[redacted]

5.8 *Subgroup analysis*

In line with the decision problem and NICE scope (Section 1.2), no subgroup analyses have been presented.

5.9 *Validation of the de novo cost-effectiveness analysis*

5.9.1 Cross-validation

The *de novo* cost-effectiveness model has been informed by previous cinacalcet cost-effectiveness models [39, 93, 94] and accounts for new data and evidence that has become available since there publication. Key differences between the *de novo* model and those used to inform the development of this are summarised in Appendix 18. As no other cost-effectiveness models of etelcalcetide were identified in the systematic literature review, it has not been possible to cross-check the results of the model presented here.

5.9.2 Face validity

To ensure face validity, several governance and review processes have been introduced. These include:

- AMGEN internal model governance processes, with reviewers of multiple disciplines.
- The involvement of an external virtual model advisory board, consisting of modelling experts in the area of calcimimetic treatment.
- A UK specific advisory board, consisting of a team of two clinicians and two health economics experts.

As a result, a broad number of experts judged the finalised economic model as clinically valid. The AMGEN internal face validity assessment took place in July 2014, July 2015 and January 2016, and involved experts in the areas of nephrology, health economics, decision-analytic modelling, and biostatistics.

The external virtual advisory board included established experts in economic evaluation has excessively reviewed draft models and the corresponding technical reports in December 2014 and in December 2015.

The UK specific advisory board consisted of two nephrologists and two health economists and convened in February 2016. The board assessed the face validity of the economic evaluation and provided extensive feedback on key assumptions and parameter inputs.

5.9.3 Technical validation

The model has been developed in-house by the AMGEN Economic Modelling Centre of Excellence. During model-development, technical validity checks have been performed

continuously. These included the confirmation of valid ranges and plausibility checks of probabilities and results. Furthermore, the members of the virtual model advisory board, in addition to their input on face validity, have reviewed both the technical report and the model itself for technical validity. They reviewed the draft versions of the economic model extensively in December 2014 and December 2015 and any issues that were identified were addressed accordingly.

Finally, the model has been quality-controlled by an external vendor. The QC was conducted following a pre-specified protocol and covered (among others) the following components:

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

5.10 *Interpretation and conclusions of economic evidence*

The objective of the economic evaluation was to assess the costs and effects of etelcalcetide (plus PB/VD) versus PB/VD alone in the anticipated broad licensed indication, and compared to cinacalcet (plus PBVD) in refractory SHPT patients with receiving HD in the UK, as per the NICE scope and decision problem (Section 1.2).

The evaluation considered all patients identified in the decision problem and is, to our knowledge, the first economic evaluation of etelcalcetide in this population.

5.10.1 Generalisability of the analysis

The analysis presented is relevant and generalisable to clinical practice in the UK. The relative treatment effect was established from the pivotal phase III etelcalcetide trials which included a total of 1706 patients across a number of locations and were considered representative of the UK population during an advisory board. All drug costs and unit costs reflect UK sources; NHS Reference costs and costs from a previous technology appraisal (NICE TA117) were used where appropriate. Utility values were derived from the EVOLVE clinical trial and reflect UK-measured preferences as a source of cost inputs. Furthermore, the model was verified for face validity by UK clinicians.

In summary, all steps have been taken to produce a robust and conservative estimate of the clinical and cost-effectiveness of etelcalcetide reflective of UK clinical practice.

5.10.2 Strengths and limitations of the economic evaluation

The modelling approach is informed by previous evaluations in the literature, namely the cost effectiveness analyses of cinacalcet conducted by PenTAG for NICE TA117 in 2007, and by Belozeroff et al in 2015. A key strength of this evaluation is that the efficacy estimates are based on a long-term data from a randomised controlled trial that directly assessed the effect of calcimimetic therapy on clinical outcomes. Although the results of the primary analysis of the EVOLVE trial—an unadjusted ITT analysis – found no statistically significant difference between cinacalcet and placebo, it is now widely recognized that treatment effect estimates were confounded by imbalances in age at randomization and high rates of discontinuation of

study drug in both cinacalcet and placebo groups. Using pre-specified, covariate-adjusted analyses that adjust for these specific confounders provides estimates of the effect-size in an "on-treatment" population. The base case etelcalcetide economic model appropriately uses these analyses of the EVOLVE trial. A further strength of the cost-effectiveness analysis is the use of EVOLVE based utility estimates, which are highly relevant and reflective of UK values.

A key assumption of the present model is that the observed proportion of patients achieving >30% PTH reduction in the etelcalcetide trials can be used to model effects on outcomes. This assumes that as the proportion achieving >30% reduction in PTH reduction with etelcalcetide in the phase III clinical trials is superior to that achieved by PB/VD alone and cinacalcet, the effects on hard outcomes for etelcalcetide are similarly affected. It is of note that NICE has previously acknowledged the relationship between biochemical parameters and adverse clinical events in SHPT, and accepted the evidence review group's approach to modelling adverse clinical events based on PTH levels in the 2007 Technology Appraisal of cinacalcet [15]. Therefore, there is a sound precedent for assuming this type of relationship. Additionally, the extrapolation approach relies on the appropriateness of a linear extrapolation of the EVOLVE hazard ratios on the log-hazard ratio scale.

To mitigate uncertainty arising from these assumptions, we have undertaken a number of different approaches to estimate the treatment effect of etelcalcetide:

- An alternative methodology for modelling hard outcomes from biochemical parameters observed in the etelcalcetide trials, utilising a published biomarker based risk-prediction equation, was used and the resulting ICERs were of the same magnitude and stable to changes in the efficacy assumptions when considering the likelihood of under or overestimating the treatment effect. This consistency with the base case model outputs provides reassurance that the base case assumptions are appropriate.

- Acknowledging the uncertainty in the extrapolated data, the model underwent extensive validation from clinical experts and health economists and the face validity of the results were confirmed.

5.10.3 Conclusion

Etelcalcetide is an innovative IV calcimimetic agent that has demonstrated superior biochemical control over placebo- and cinacalcet-based regimens in the treatment of SHPT patients on HD. It has robustly demonstrated clinically meaningful and superior SHPT control over placebo and cinacalcet when added to PB/VD across the broad population of SHPT patients meeting its licensed indication, and in those with SHPT that is refractory to PB/VD alone.

Etelcalcetide is well tolerated with an adverse event profile consistent with the pre-existing comorbid conditions typically associated with SHPT and the mechanism of action of calcimimetics. This favourable benefit-risk profile, coupled with the ease of IV administration at the end of dialysis (giving specialists flexibility and control over delivery) means that etelcalcetide represents a significant advance over existing therapies.

The economic evaluation presented in this submission reflects the NICE scope-defined comparisons of etelcalcetide at its anticipated list price. The clinical effectiveness data used to inform the evaluation was generalisable to the UK, cost and unit resource inputs reflected UK clinical practice, and the model underwent extensive validation checks with UK-based nephrologists. In its broad licensed indication, etelcalcetide (plus PB/VD) has an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained compared with PB/VD regimens alone. In patients with refractory SHPT, etelcalcetide (plus PB/VD) has an ICER of [redacted]

per QALY gained compared with cinacalcet (plus PB/VD). Extensive sensitivity and scenarios were employed across both comparisons to explore the uncertainty in the evaluation and demonstrated that the results are robust to changes in model parameters.

Amgen proposes that etelcalcetide be recommended as a treatment option for patients with SHPT with chronic kidney disease, receiving haemodialysis.

6 Assessment of factors relevant to the NHS and other parties

6.1 *Aims*

A budget impact model has been developed to explore the impact of etelcalcetide on NHS budget over a 5-year time period. The inputs of the budget impact model are, where possible, aligned with the cost-effectiveness model presented in Section 5. However, some parameters are specific for the budget impact analysis only. These include estimates of the eligible patient population and market share estimates prior to and after etelcalcetide is recommended for use in the NHS. The key components of the budget impact model are explored in more detail below.

6.2 *Patient population*

The number of patients with SHPT receiving haemodialysis (HD) treatment for ESRD and eligible for etelcalcetide treatment is estimated in a stepwise approach. The parameters and the sources are provided in Table 77.

To determine the prevalence of adults with SHPT in the HD population, a targeted literature search was conducted. These searches identified a recent systematic literature review by Hedgeman *et al* 2015 which determined that 42.9% of the HD population were diagnosed with SHPT in the UK (defined as PTH>300 pg/ml). The authors of the study contacted a number of national societies of nephrology between July and August 2013 for information on the prevalence of SHPT available from renal registries and other locally identified sources. Included in these data were SHPT prevalence data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [3].

An estimate of the total eligible patient population for etelcalcetide was calculated from the SHPT population by accounting for both the number of patients likely to undergo parathyroidectomy and those with adjusted Ca levels <2.2mmol/L. [redacted]

Table 77: Population size parameters

Parameter	England	Wales	Source
Number of adult HD patients, 2014	20,565	1,115	UK Renal Report 18th; Table 2.2 [62]
Annual increase of dialysis population*	1.00%	1.00%	UK Renal Report 18th; Table 2.2 [62]
Number of adult HD patients , 2017	20,978	1,137	Calculated
Percentage of adult HD patients with SHPT	42.9%		Hedgeman *et al*. 2015 [3]
Number of adult HD patients with SHPT	9,000	488	Calculated
Number of adult patients with SHPT receiving parathyroidectomy (annually)	122	7	HES 2015-16** [147]
Percentage of patients with adjusted Ca <2.2mmol/L	10.60%	11.90%	UK Renal Report 18th; Table 9.8 [62]

Number eligible for etelcalcetide	7,937	424	Calculated
Total	**8,360**		Calculated

DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, haemodialysis; PTH, parathyroid hormone; UK, United Kingdom
* Change in UK HD prevalence rates (assume same for England and Wales)
** Assumed consistent rate in Wales

6.3 *Current treatment options and uptake*

The estimated market shares prior to and post the availability of etelcalcetide are presented in Table 78. Current market share estimates are based on the existing cinacalcet market penetration and is aligned with the treatment pathway presented in Section 3.3, where cinacalcet is used as an add-on therapy for patients who are refractory to PB/VD alone. Market share estimates for cinacalcet and PB/VD alone are assumed to remain largely consistent over the duration of the model.

In the post-implementation scenario, etelcalcetide in addition to PB/VD is assumed to displace both PB/VD alone and cinacalcet (in the refractory population). This is aligned with the NICE final scope, the positioning presented in Section 3.3, and the pair-wise economic comparisons discussed in Section 5.2.3. It is assumed that the majority of etelcalcetide market share would be derived from displacing cinacalcet in the refractory population as this reflects current calcimimetic use in the UK. Nevertheless, as etelcalcetide may be used as an add-on to PB/VD prior to patients becoming refractory (e.g. to achieve improved biochemical control), this is reflected below.

Table 78: Estimated market dynamics

	2017	2018	2019	2020	2021
Estimated current market shares					
Share of patients on cinacalcet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Share of patients on PB/VD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated market shares after implementation of etelcalcetide					
Share of patients on etelcalcetide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Share of patients on cinacalcet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Share of patients on PB/VD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PB, phosphate binder; VD, Vitamin D

6.4 *Model parameters*

The budget impact model investigates the cost and resource use associated with etelcalcetide (plus PBVD) for the treatment of SHPT. The model is aligned with the cost-effectiveness evaluation and takes into account the following parameters:

- Drug prices and unit costs (see Section 5.4.1)
- Treatment efficacy (see Section 5.2.6.3)
- Resource consumption by treatment group (see Section 5.4.2–5.4.4)

All inputs listed above – with the exception of the baseline event rates – are consistent with the base case parameters used in the economic evaluation which are summarised in Table 53.

The baseline event rates for non-fatal CV, non-fatal fracture and PTx differ slightly from those used in the economic evaluation as the BIM is not structured using health states. As such, an overall incidence rate is applied rather than using initial and subsequent event rates. For consistency with the economic evaluation, these rates are also derived from the placebo arm of the EVOLVE trial using the lag-censored estimates and are presented in Table 79 below.

Table 79: Baseline event rates (events per person year)

Parameter	Estimate	Source
Non-fatal CV[1]	[redacted]	EVOLVE trial, placebo arm; Lag-censored event rates. Table 12.9.1 [118]
Non-fatal fracture		
PTx		

CV, cardiovascular; PTx, parathyroidectomy
[1] Myocardial infarction, unstable angina, heart failure and peripheral vascular event

6.5 *Results*

The table below presents the estimated total numbers of patients treated with each comparator in the prior to and post-implementation of etelcalcetide scenarios (Table 80). The total number of patients treated increases marginally over the model time horizon due to anticipated annual growth of 1.0% in the dialysis population (independent of the implementation of etelcalcetide).

Table 80: Estimated total number of patients treated with each comparator

	2017	2018	2019	2020	2021
Total number of patients treated					
Total subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No implementation of etelcalcetide					
Subjects on cinacalcet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects on PB/VD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
After implementation of etelcalcetide					
Subjects on etelcalcetide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects on cinacalcet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects on PB/VD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PB, phosphate binder; VD, Vitamin D

In Table 81, the occurrence of each type of event (CV, fracture and PTx) is displayed per year both before and after implementation of etelcalcetide. The number of clinical events in the new situation is lower as etelcalcetide is associated with lower event rates compared cinacalcet and PB/VD alone (see Table 34).

Table 81: Comparison of clinical events per year

	2017	2018	2019	2020	2021
No implementation of etelcalcetide					
No of CV events	810	816	824	832	840
No of Fx events	235	236	239	241	243
No of PTx events	191	191	193	195	197
After implementation of etelcalcetide					
No of CV events	808	809	806	805	813
No of Fx events	234	234	234	233	236
No of PTx events	190	188	183	179	181

CV, cardiovascular; Fx, fracture; PTx, parathyroidectomy

Table 82 shows the cost components for both situations for each year. Calcimimetic drug cost are increased in the new market situation, as the total number of patients using calcimimetics has increased. The total PB/VD costs remains the same as the usage is set equal for all treatments. The additional drug costs are partly compensated by cost-offsets due the reduction in clinical events.

Table 82: Comparison of cost components per year

	2017	2018	2019	2020	2021
No implementation of etelcalcetide					
Calcimimetics	£9,966,718	£10,353,996	£10,457,536	£10,562,112	£10,667,733
Phosphate binders	£7,376,486	£7,450,251	£7,524,754	£7,600,001	£7,676,001
Vitamin D	£5,347,778	£5,401,256	£5,455,268	£5,509,821	£5,564,919
Event costs	£3,516,051	£3,533,535	£3,568,870	£3,604,559	£3,640,604
Total costs	**£26,207,033**	**£26,739,038**	**£27,006,428**	**£27,276,493**	**£27,549,258**
After implementation of etelcalcetide (list price)					
Calcimimetics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phosphate binders	£7,376,486	£7,450,251	£7,524,754	£7,600,001	£7,676,001
Vitamin D	£5,347,778	£5,401,256	£5,455,268	£5,509,821	£5,564,919
Event costs	£3,502,919	£3,495,209	£3,461,694	£3,439,183	£3,473,575
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The total estimated incremental impact of implementation of etelcalcetide is presented in Table 83. It shows that reimbursement of etelcalcetide results in an estimated incremental budget impact of approximately £503K to £ 7.2M from year 1 to 5, and a cumulative impact of £21.5M over the 5-tyear period.

Table 83: Incremental budget impact of implementation of etelcalcetide

	2017	2018	2019	2020	2021
Budget impact: list price					
Calcimimetics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phosphate binders	£0	£0	£0	£0	£0
Vitamin D	£0	£0	£0	£0	£0
Event costs	-£13,132	-£38,325	-£107,176	-£165,375	-£167,029
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CV, cardiovascular; PTx, parathyroidectomy

7 References

1. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clinical journal of the American Society of Nephrology : CJASN. 2011;6(4):913-21.
2. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. Kidney international. 2008;74(3):276-88.
3. Hedgeman E, Lipworth L, Lowe K, Saran R, Do T, Fryzek J. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. International journal of nephrology. 2015;2015:184321.
4. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. Journal of the American Society of Nephrology : JASN. 2004;15(8):2208-18.
5. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2011;26(6):1948-55.
6. Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney international. 2006;70(7):1358-66.
7. Natoli JL, Boer R, Nathanson BH, Miller RM, Chiroli S, Goodman W, et al. Is there an association between elevated or low serum levels of phosphorus, parathyroid hormone, and calcium and mortality in patients with end stage renal disease? A meta-analysis. BMC nephrology. 2013;14(14):88.
8. Malindretos P, Sarafidis P, Lazaridis A, Nikolaidis P. A study of the association of higher parathormone levels with health-related quality of life in hemodialysis patients. Clin Nephrol. 2012;77(03):196-203.
9. Chiroli S, Mattin C, Belozeroff V, Perrault L, Mitchell D, Gioni I. Impact of mineral and bone disorder on healthcare resource use and associated costs in the European Fresenius medical care dialysis population: a retrospective cohort study. BMC nephrology. 2012;13:140.
10. Lee A, Belozeroff V, Song X, Diakun D, Goodman W. Costs of Treatment and Clinical Events for Secondary Hyperparathyroidism. Am J Pharm Benefits. 2013;5(2):e24-e35.
11. KDIGO. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney international Supplement. 2009(113):S1-130.
12. Cozzolino M, Tomlinson J, Walsh L, Bellasi A. Emerging drugs for secondary hyperparathyroidism. Expert opinion on emerging drugs. 2015;20(2):197-208.
13. Moe SM, Drueke TB. Management of secondary hyperparathyroidism: the importance and the challenge of controlling parathyroid hormone levels without elevating calcium, phosphorus, and calcium-phosphorus product. American journal of nephrology. 2003;23(6):369-79.
14. Fissell R, Karaboyas A, Bieber B, al. e. Phosphate binder pill burden, patient-reported non-adherence, and mineral bone disorder markers: Findings from the DOPPS. . Hemodialysis International 2016;20:38-49.
15. NICE. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. NICE technology appraisal guidance 117. 2007.

16. Adelphi Research UK. SHPT Patient Pathway Research (PP22891). 2016.
17. Block GA, Martin KJ, De Francisco A, Turner SA, Avram MM. Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis. The New England journal of medicine. 2004;350:1516-25.
18. Park H, Rascati KL, Lawson KA, Barner JC, Richards KM, Malone DC. Adherence and persistence to prescribed medication therapy among Medicare part D beneficiaries on dialysis: comparisons of benefit type and benefit phase. J Manag Care Pharm. 2014;20(8):862-76.
19. Reams B, Dluzniewski P, Do T, Yue S, Bradbury B, Kshirsagar AV, et al. Dynamics of cinacalcet use and biochemical control in hemodialysis patients: A Retrospective New-User Cohort Design. BMC nephrology. 2015;16:175.
20. Belozeroff V, Cooper K, Hess G, Chang CL. Healthcare use and costs before and after parathyroidectomy in patients on dialysis. BMC health services research. 2013;13(1):248.
21. Wetmore JB, Jiannong L, Do T, Lowe K, Ishani A, Bradbury B, et al. Changes in Secondary Hyperparathyroidism-Related Biochemical Parameters and Medication Use Following Parathyroidectomy Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2016;31(1):103-11.
22. NICE. Single Technology Appraisal: Etelcalcetide for treating secondary hyperparathyroidism - Final scope for invitation (Appendix B). 2016.
23. Amgen. Parsabiv - EU Summary of Product Characteristics (DRAFT). 2016.
24. NICE. Etelcalcetide for treating secondary hyperparathyroidism: Response to consultee and commentator comments on the draft remit and draft scope (pre-referral) 2016.
25. European Medicines Agency. CHMP Assessment Report: Parsabiv (draft). 2016.
26. Alexander ST, Hunter T, Walter S, Dong J, Maclean D, Baruch A, et al. Critical cysteine residues in both the calcium-sensing receptor and the allosteric activator AMG 416 underlie the mechanism of action. Molecular pharmacology. 2015;88(5):853-65.
27. European Medicines Agency. CHMP Summary of opinion (initial authorisation): Parsabiv (Etelcalcetide). 2016.
28. Amgen. 20120229 Clinical Study Report. 2014.
29. Amgen. 20120230 Clinical Study Report. 2014.
30. Amgen. 20120360 Clinical Study Report. 2015.
31. Amgen. AMG 416 Summary of Clinical Efficacy. 2015.
32. Amgen. 20120231 Clinical Study Report. 2015.
33. Amgen data on file. Study 20130213 Interim analysis summary. 2016. 2016.
34. Amgen. AMG 416 Summary of Clinical Safety. 2015.
35. Amgen data on file. Mimpara presistence and compliance: Italy. IMS Health Project 1088528. 2016.
36. Amgen data on file. Mimpara presistence and compliance: France. IMS Health Project 1088528. 2016.
37. Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. The New England journal of medicine. 2012;367(26):2482-94.
38. Kubo Y, Sterling LR, Parfrey PS, Gill K, Mahaffey KW, Gioni I, et al. Assessing the treatment effect in a randomized controlled trial with extensive non-adherence: the EVOLVE trial. Pharmaceutical statistics. 2015;14(4):368.
39. Eandi M, Pradelli L, Iannazzo S, Chiroli S, Pontoriero G. Economic Evaluation of Cinacalcet in the Treatment of Secondary Hyperparathyroidism in Italy. Pharmacoeconomics. 2010;28(11):1041-54.
40. Amgen. Mimpara (cinacalcet) Summary of Product Characteristics, EMA. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-

_Product_Information/human/000570/WC500028900.pdf (access date 6 July 2015). 2015 [6 July 2015]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000570/WC500028900.pdf.
41. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. Clinical journal of the American Society of Nephrology : CJASN. 2009;4(6):1089-96.
42. Reams D, Dluzniewski P, Kshirsagar AV, Bradbury B, Walsh L, Brookhart M. The Effect of Cinacalcet Persistence on Risk of All-Cause Mortality and Heart Failure (Abstract submitted to ASN 2015 meeting). 2015.
43. NICE. Chronic kidney disease in adults: assessment and management (CG182). 2015.
44. Hauber B, Posner J, Moon K. Preferences for the Management of Anemia and Secondary Hyperparathyroidism in Patients With Chronic Renal Failure Undergoing Hemodialysis: SHPT Results Memorandum. RTI-HS Project No. 0303911. 2016.
45. Block GA, Kilpatrick RD, Lowe KA, Wang W, Danese MD. CKD-Mineral and Bone Disorder and Risk of Death and Cardiovascular Hospitalization in Patients on Hemodialysis. Clinical journal of the American Society of Nephrology : CJASN. 2013.
46. Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SH, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. Clinical journal of the American Society of Nephrology : CJASN. 2015;10(1):98-109.
47. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international. 2006;69(11):1945-53.
48. Saliba W, El-Haddad B. Secondary hyperparathyroidism: pathophysiology and treatment. Journal of the American Board of Family Medicine : JABFM. 2009;22(5):574-81.
49. Blayney MJ, Pisoni RL, Bragg-Gresham JL, Bommer J, Piera L, Saito A, et al. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. Kidney international. 2008;74(5):655-63.
50. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney international. 2007;71(5):438-41.
51. Shantouf RS, Budoff MJ, Ahmadi N, Ghaffari A, Flores F, Gopal A, et al. Total and individual coronary artery calcium scores as independent predictors of mortality in hemodialysis patients. American journal of nephrology. 2010;31(5):419-25.
52. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension. 2001;38:938-42.
53. Fernandez-Martin JL, Martinez-Camblor P, Dionisi MP, Floege J, Ketteler M, London G, et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2015;30:1542-51.
54. Danese M, Halperin M, Lowe K, al. e. Refining the definition of clinically important mineral and bone disorder in hemodialysis patients. . Nephrol Dial Transplant 0: 1–9. 2015.
55. Danese MD, Belozeroff V, Smirnakis K, Rothman KJ. Consistent control of mineral and bone disorder in incident hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN. 2008;3(5):1423-9.
56. Parfrey P, Chertow B, Block G, al. e. The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of

cinacalcet: The EVOLVE Trial. The Journal of clinical endocrinology and metabolism. 2013;98(4834-44).
57. Briggs AH, Parfrey P, Khan N, Tseng S, Dehmel B, Chertow GM, et al. The effects of study events and treatment on health-related quality of Life (HRQoL) in the EVOLVE trial. Poster presented at American Society of Nephrology Annual Meeting 5-10 November 2013, Atlanta, GA. 2013.
58. Davies EW, Matza LS, Worth G, Feeny DH, Kostelec J, Soroka S, et al. Impact of major clinical events on utilities in the context of secondary hyperparathyroidism (SHPT) and chronic kidney disease (CKD) treated with dialysis. Poster presented at ISPOR 16th Annual Congress, 2-6 November 2013, Dublin, Ireland. 2013.
59. Chertow GM, Lu ZJ, Xu X, Knight TG, Goodman WG, Bushinsky DA, et al. Self-reported symptoms in patients on hemodialysis with moderate to severe secondary hyperparathyroidism receiving combined therapy with cinacalcet and low-dose vitamin D sterols. Hemodialysis international International Symposium on Home Hemodialysis. 2011;16(2):188-97.
60. Johansen KL, Chertow GM. Chronic kidney disease mineral bone disorder and health-related quality of life among incident end-stage renal-disease patients. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2007;17(5):305-13.
61. Arbor Research Collaborative for Health. 2012 Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data 1997-2011. http://www.dopps.org/AnnualReport/ (access date June 2015). 2012. Available from: http://www.dopps.org/AnnualReport/.
62. UK Renal Registry. 18th Annual Report. 2016.
63. Owda A, Elhwairis H, Narra S, Towery H, Osama S. Secondary Hyperparathyroidism in Chronic Hemodialysis Patients: Prevalence and Race. Renal Failure. 2003;25(4):595-602.
64. Gutierrez O, Isakova T, Andress D, al. e. Prevalence and severity of disordered mineral metabolism in Blacks with chronic kidney disease. Kidney international Supplement. 2008;73(8):956-62.
65. NICE. Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia. NICE CG 157. 2013.
66. UK Renal Association. Clinical Practice Guideline: CKD-Mineral and bone disorder (CKD-MBD). 2015.
67. Goldsmith DJ, Covic A, Fouque D, Locatelli F, Olgaard K, Rodriguez M, et al. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(12):3823-31.
68. Steddon S, Sharples E. How do the KDIGO Clinical Practice Guidelines on CKD - MBD apply to the UK? UK Renal Association, 2013.
69. Kilpatrick RD, Danese MD, Belozeroff V, Smirnakis K, Goodman WG, Rothman KJ. The association of vitamin D use with hypercalcemia and hyperphosphatemia in hemodialysis patients: a case-crossover study. Pharmacoepidemiology and drug safety. 2011;20(9):914-21.
70. Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder G, Strippoli GF. Meta-analysis: vitamin D compounds in chronic kidney disease. Ann Intern Med. 2007;147:840-53.
71. BMJ Group / Pharmaceutical Press. British National Formulary; September 2016 2016 [11/10/2016]. Available from: https://www.medicinescomplete.com/mc/bnf/current/index.htm.
72. Massry S, Coburn J, Chertow G, Hruska K, Langman C, Malluche H, et al. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney

disease. . American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;42(4 suppl 3):i-S201.
73. Cunningham J, Danese MD, Olson K, Klassen P, Chertow GM. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney international. 2005;68:1793-800.
74. NICE. Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence (NICE). https://www.nice.org.uk/article/pmg9 (access date June 2015). 2013.
75. Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, et al. The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation. Health technology assessment. 2007;11(18):iii, xi-xiii, 1-167.
76. Cunningham J, editor A Long Acting Intravenous Calcimimetic (AMG 416) for Secondary Hyperparathyroidism (SHPT) in Haemodialysed Patients. 52nd ERA-EDTA Congress; 2015 29 May 2015; London, UK.
77. Martin K, Block G, Cheng S, Dehmel B, Kewalramani R, Spiegel D, et al. Comparison of the Efficacy and Safety of Intravenous (IV) Etelcalcetide (AMG 416) and Oral Cinacalcet in Patients on Hemodialysis With Secondary Hyperparathyroidism; SA-PO1115. American Society of Nephrology; November 3–8, 2015; San Diego, CA2015.
78. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 2011 [07/10/2016]. Available from: http://handbook.cochrane.org/.
79. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. 2009.
80. Behets G, Spasovski G, Sterling L, Goodman W, Spiegel D, De Broe M, et al. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015;87(4):846-56.
81. Moe S. Current issues in the management of secondary hyperparathyroidism and bone disease. Perit Dial Int. 2001;21(Suppl 3):S241-6.
82. Gutierrez O, Mannstadt MD, Isakova T, al e. Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis. The New England journal of medicine. 2008;359:584-92.
83. Amgen data on file. Parsabiv® preliminary data for 2nd-line treatment after cinacalcet 'failure'. . 2016.
84. Amgen. 20120359 Clinical Study Report. 2014.
85. Liss K, Block G, Chertow G, Dehmel B, Sun Y, Spiegel D. Initiation of AMG 416 (Etelcalcetide) After Discontinuation of Cinacalcet; TH-PO871. American Society of Nephrology; November 3–8, 2015; San Diego, CA2015.
86. Bushinsky D, Block G, Cheng S, Deng H, Ureña-Torres P, Vervloet M, et al., editors. One Year Efficacy and Safety of Intravenous Etelcalcetide (AMG 416) in Patients on Hemodialysis with Secondary Hyperparathyroidism (Study 20120231). 53rd ERA-EDTA Congress; 2016 21-24 May 2016; Vienna, Austria.
87. Martin Kea. Interim analysis of a multicentre single-arm extension study to describe the long-term safety of etelcalcetide (AMG416) in the treatment of secondary hyperparathyroidism in subjects with chronic kidney disease on hemodialysis. Abstract TH-PO527 ASN Kidney Week 2016, Chicago IL, 15-20 November 2016 2016.
88. Amgen. AMG 416 Clinical Overview. 2015.
89. National Kidney Foundation. Parathyroid Hormone and Secondary Hyperparathyroidism in Chronic Kidney Disease: Stage 5D. 2012.
90. Reams B data on file. 2015.
91. Komaba H, Moriwaki K, Goto S, Yamada S, Taniguchi M, Kakuta T, et al. Cost-effectiveness of cinacalcet hydrochloride for hemodialysis patients with severe

secondary hyperparathyroidism in Japan. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60(2):262-71.
92. Nuijten M, Roggeri DP, Roggeri A, Novelli P, Marshall TS. Health Economic Evaluation of Paricalcitol® Versus Cincalcet+ Calcitriol (Oral) in Italy. Clinical drug investigation. 2015;35(4):229-38.
93. Garside R, Pitt M, Anderson R, Mealing S, D'Souza R, Stein K. The cost-utility of cinacalcet in addition to standard care compared to standard care alone for secondary hyperparathyroidism in end-stage renal disease: a UK perspective. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2007;22(5):1428-36.
94. Belozeroff V, Chertow GM, Graham CN, Dehmel B, Briggs AH. Economic evaluation of cinacalcet in the United States: the EVOLVE trial. Value in Health (accepted). 2015.
95. Rosery H, Bergemann R, Marx S, al e. Health-Economic Comparison of Paricalcitol, Calcitriol and Alfacalcidol for the Treatment of Secondary Hyperparathyroidism during Haemodialysis. Clinical drug investigation. 2006;26(11):629-38.
96. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. Journal of the American Society of Nephrology : JASN. 2013;24(9):1461-9.
97. Teng M, Wolf M, Lowrie EG, Ofsthun N, Lazarus JM, Thadhani R. Survival of Patients Undergoing Hemodialysis with Paricalcitol or Calcitriol Therapy. The New England journal of medicine. 2003;349:446-56.
98. Schumock GT WS, Lee TA, Marx SE, Audhya P, Andress DL. Comparative effectiveness of paricalcitol versus cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. Nephron 2011;117(2):c151-9. 2011.
99. Narayan R, Perkins RM, Berbano EP, Yuan CM, Neff RT, Sawyers ES, et al. Parathyroidectomy versus cinacalcet hydrochloride-based medical therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2007;49(6):801-13.
100. Ray JA, Borker R, Barber B, Valentine WJ, Belozeroff V, Palmer A. Cost-Effectiveness of Early versus Late CinacalcetTreatment in Addition to Standard Care for Secondary Renal Hyperparathyroidism in the USA. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2008.
101. Eandi M. A patient-level simulation model for economic evaluation of cinacalcet in the treatment of secondary hyperparathyroidism (SHPT) in Italy. Presented at ISPOR 12th Annual European Congress; 24-27 Oct 2009; Paris, France Value Health 2009;12(7):A406. 2009.
102. Gordois A. Paricalcitol is cost-effective in treating secondary hyperparathyroidism in people with chronic kidney disease. . Presented at 47th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology; 19-21 Sept 2011; Adelaide, SA Australia Nephrology 2011;16:64. 2011.
103. Iannazzo S, Carsi M, Sorio F, Chiroli S. Análisis de coste-utilidad de cinacalcet en el hiperparatiroidismo secundario en España. PharmacoEconomics - Spanish Research Articles 2011;8(3):99-110.
104. Iannazzo S, Carsi M, Chiroli S. A cost-utility analysis of cinacalcet in secondary hyperparathyroidism in five European countries. Applied health economics and health policy. 2012;10(2):127-38.
105. Boer R, Lalla AM, Belozeroff V. Cost-effectiveness of cinacalcet in secondary hyperparathyroidism in the United States. Journal of medical economics. 2012;15(3):509-20.
106. Fukagawa M, Yumita S, Akizawa T, Uchida E, Tsukamoto Y, Iwasaki M, et al. Cinacalcet (KRN1493) effectively decreases the serum intact PTH level with favorable control of the serum phosphorus and calcium levels in Japanese dialysis

patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2008;23(1):328-35.
107. Menezes FG NM, Peixoto RB,. Cost-effectiveness of paricalcitol in end stage chronic kidney disease secondary hyperparathyroidism patients on dialysis, in Brazil. Presented at ISPOR 4th Latin America Conference; 12-14 Sept 2013; Buenos Aires, Argentina Value in Health 2013;16(7):A698. 2013.
108. Nishikawa AM CM, Custodio MR, Pecoits-Filho RF, Clark OAC. Cost-effectiveness of cinacalcet chronic kidney disease patients on dialysis with secondary hyperparathyroidism in Brazilian public health care system (SUS). Presented at ISPOR 4th Latin America Conference; 12-14 Sept 2013; Buenos Aires, Argentina Value in Health 2013;16(7):A698. 2013.
109. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Med Decis Making. 2012;32(5):690-700.
110. Barendregt JJ. The half-cycle correction: banish rather than explain it. Med Decis Making. 2009;29(4):500-2.
111. Naimark DM, Kabboul NN, Krahn MD. Response to "the life table method of half-cycle correction: getting it right". Med Decis Making. 2014;34(3):286-7.
112. Urena P, Jacobson SH, Zitt E, Vervloet M, Malberti F, Ashman N, et al. Cinacalcet and achievement of the NKF/K-DOQI recommended target values for bone and mineral metabolism in real-world clinical practice--the ECHO observational study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2009;24(9):2852-9.
113. Stollenwerk B, Dehmel B, Akehurst R, Parfrey P, Briggs A, Iannazzo S, et al. Modelling etelcalcetide effectiveness on health outcomes: Relating biochemical outcomes to mortality, cardiovascular events, fractures and parathyroidectomy. Society for Medical Decision Making (SMDM), 16th Biennial European Conference; June 14, 2016; London2016.
114. NICE Decision Support Unit. Technical support document 16: Adjusting survival time estimates in the presence of treatment switching. 2014.
115. Kleinbaum DG, Klein M. Survival analysis. New York: Springer; 1996.
116. Efron B, Tibshirani RJ. An introduction to the bootstrap. Boca Raton: CRC press; 1994.
117. Amgen. Baseline mortality rates. Data on file. 2016.
118. Amgen. Baseline initial clinical event rates. Data on file. 2016.
119. Amgen. Baseline subsequent clinical event rates. Data on file. 2016.
120. Briggs A, Parfrey P, Khan N, al. e. Analyzing Health-Related Quality of Life in the EVOLVE Trial: The Joint Impact of Treatment and Clinical Events. Med Decis Making. 2016: pii: 0272989X16638312. [Epub ahead of print].
121. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health policy. 1990;16(3):199-208.
122. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.
123. Davies EW, Matza LS, Worth G, Feeny DH, Kostelec J, Soroka S, et al. Health state utilities associated with major clinical events in the context of secondary hyperparathyroidism and chronic kidney disease requiring dialysis. Health and quality of life outcomes. 2015;13(1):1.
124. Lun L LD, Li X, Wei X, Miao J, Gao Z, et al. Effects of parathyroidectomy on quality of life in uremic patients with secondary hyperparathyroidism. Presented at 51st ERA-EDTA Congress; 31 May- 3 June 2014; Amsterdam, Netherlands Nephrol Dial Transplant 2014;29:iii270. 2014.

125. Filipozzi P, Ayav C, Erpelding ML, Kessler M, Brunaud L, Frimat L. Influence on quality of life from an early cinacalcet prescription for secondary hyperparathyroidism in dialysis. Pharmacoepidemiology and drug safety. 2015;24(2):187-96.
126. Stollenwerk B, Stock S, Siebert U, Lauterbach KW, Holle R. Uncertainty assessment of input parameters for economic evaluation: Gauss's error propagation, an alternative to established methods. Med Decis Making. 2010;30(3):304-13.
127. Duenas A FJ, Rawdin A, Wilkie M, Harrison B, Akehurst R. Assessing the cost of parathyroidectomy as a treatment for uncontrolled secondary hyperparathyroidism in stage 5 chronic kidney disease. Paper presented at 17th ERA-EDTA Congress - II DGfN Congress; 25-28 June 2010; Munich, Germany NDT Plus 2010;3(iii98-iii99). 2010.
128. Pockett RD, Cevro E, Scott-Coombes D, Chamberlain G. Assessment of the Resource Use and Costs Associated with Parathyroidectomy Surgery for Secondary Hyperparathyroidism in End Stage Renal Disease in the UK - poster. ISPOR. 2012.
129. Pockett RD, Cevro E, Chamberlain G, Scott-Coombes D, Baboolal K. Assessment of Resource Use and Costs Associated with Parathyroidectomy for Secondary Hyperparathyroidism in End Stage Renal Disease in the UK. Journal of medical economics. 2014;17(198-206).
130. Lee A, Song X, Belozeroff V, Diakun D, Goodman W. Costs of Care and Major Clinical Events Among Chronic Dialysis Patients With and Without Treatment for sHPT: A Descriptive Study of Claims Data - poster. ASN. 2011.
131. Belozeroff V, Chertow GM, Graham CN, Dehmel B, Briggs AH. Economic evaluation of cinacalcet in the United States: the EVOLVE trial. Supplementary Material. Value in Health. 2015.
132. Amgen. Average Dose of Calcimimetic Drugs during the Efficacy Assessment Phase. Data on file. 2016.
133. Floege J, Raggi P, Block GA, Torres PU, Csiky B, Naso A, et al. Study design and subject baseline characteristics in the ADVANCE Study: effects of cinacalcet on vascular calcification in haemodialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(6):1916-23.
134. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2011;26(4):1327-39.
135. Amgen. Use of Active Vitamin D – pooled. Data on File. 2016.
136. 2016. Available from: https://www.bnf.org/.
137. Tariff NED. April 2016. Available from: http://www.drugtariff.nhsbsa.nhs.uk/.
138. Prescription Cost Analysis E. 2015. Available from: http://www.hscic.gov.uk/catalogue/PUB20200.
139. Service NH. National Schedule of Reference Costs 2014-2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
140. PSSRU. Unit Costs of Health and Social Care 2015. 2015.
141. Grima DT, Mendelssohn D, McFarlane P, Dunn E. INCLUSION OF DIALYSIS COSTS IN COST-EFFECTIVENESS ANALYSES OF THERAPIES FOR PATIENTS ON DIALYSIS: A CASE STUDY OF SEVELAMER FOR THE TREATMENT OF HYPERPHOSPHATEMIA - abstract. 2012.
142. Amgen. Frequency and Type of Dialysis. Data on file. 2016.
143. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation: OUP Oxford; 2006.
144. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making. 1985;5(2):157-77.

145. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied Methods of Cost-effectiveness Analysis in Healthcare: OUP Oxford; 2010.
146. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.
147. Digital NHS. Hospital Episode Statistics (HES). Available at: http://content.digital.nhs.uk/hes. 2016.
148. Chertow GM, Pupim LB, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview. Clinical journal of the American Society of Nephrology : CJASN. 2007;2(5):898-905.
149. Danese MD, Kim J, Doan QV, Dylan M, Griffiths R, Chertow GM. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2006;47(1):149-56.
150. Amgen. Event based average persistence EVOLVE. Data on file. 2016.
151. Amgen. Summary of Persistence in etelcalcetide trials. Data on file. 2015.
152. Eandi M, Pradelli L, Iannazzo S, Chiroli S, Pontoriero G. Economic Evaluation of Cinacalcet in the Treatment of Secondary Hyperparathyroidism in Italy (Supplemental Digital Content). PharmacoEconomics. 2010;28(11):1041-54.
153. Kintner HJ. The life table. In: Siegel JS, Swanson DA, editors. The Methods and Materials of Demography. San Diego: Elsevier Academic Press; 2004.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Etelcalcetide for the treatment of secondary hyperparathyroidism [ID908]

Patient access scheme submission

Prepared by:

AMGEN

File name	Version	Contains confidential information	Date
	1.2	Yes redacted	06th February 2017

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: Etelcalcetide (Parsabiv®)

Disease area: Secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy

3.2 Please outline the rationale for developing the patient access scheme.

The rationale behind the patient access scheme (PAS) is to mitigate any uncertainty associated with analysis of cost-effectiveness presented in company submission of evidence to NICE.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The proposed PAS is a simple scheme (confidential discount of the NHS list price of each etelcalcetide vial). The proposed confidential discount is [redacted] The scheme is expected to be implemented at the time of positive (or draft positive) NICE guidance.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS applies to the whole population for which etelcalcetide is licensed, i.e. for the treatment of SHPT in adult patients with CKD on haemodialysis therapy

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any additional criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Not applicable.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The price (including the PAS confidential discount) will be demonstrated to NHS organisations on the original invoice.

No additional information will need to be collected.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See above.

3.10 Please provide details of the duration of the scheme.

The PAS will remain in place until NICE next reviews the product under the technology appraisals programme and any final decision has been published by NICE (as per the declaration signed by Amgen in the PAS proposal template).

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The PAS does not require completion of any forms or other administrative process.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The PAS applies to the entire licensed population for etelcalcetide, which covers the populations presented in the main submission of evidence.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The PAS is likely to be approved prior to the first Appraisal Committee meeting. No changes relating to assumptions have been made to the model.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The confirmed list price has changed from what was presented in the main evidence submission thus results for both the updated list price and with application of the patient access scheme are presented in this addendum.

The confirmed list price for etelcalcetide is presented alongside the prices with the patient access scheme below.

Table 1: List and PAS price of etelcalcetide vials

Product	Dose	Presentation	Pack Size	NHS list price	PAS price
Etelcalcetide (Parsabiv®)	2.5 mg	2.5 mg in 0.5 ml solution	x6 vials	£136.87 per pack	[redacted]
Etelcalcetide (Parsabiv®)	5 mg	5 mg in 1 ml solution	x6 vials	£163.92 per pack	[redacted]
Etelcalcetide (Parsabiv®)	10 mg	10 mg in 2 ml solution	x6 vials	£327.84 per pack	[redacted]

The economic model requires the etelcalcetide price to be entered in a per mg unit on the 'Input Costs' sheet of the executable model file. As the per mg price varies between vial sizes, a weighted average is calculated based on the vial distribution across the etelcalcetide clinical trials (study 20120229, study 20120230 and study 20120360). The analysis is aligned with the drug use assumptions presented in the main submission (ie. based on the safety analysis set of the trials and quantified during the efficacy assessment phase [EAP]) and the results have been presented in Table 2, below.

Table 2: Distribution of dose of etelcalcetide during EAP in etelcalcetide trials

Dose (mg)	Frequency
2.5	[redacted]
5	
7.5	
10	
12.5	
15	
Vial Distribution	
2.5	[redacted]
5	
10	

Subjects enrolled in studies 20120229 and 20120230, and 20120360 randomised to receive AMG416.
Safety analysis set: all subjects in the pool who received at least one non-missing dose of IP and exclude subjects who received commercial use of cinacalcet.
Dose assumed to be given using the minimum number of vials.
Three doses were recorded erroneously (1 instance of 9 mg and 2 instances of 9.5 mg) and were excluded from the analysis

The weighted list price of etelcalcetide implemented in the economic model is [redacted]. Applying the confidential discount of [redacted] to the list price of each vial results in a with-PAS per mg price of [redacted] implemented in the model. Results have been presented for both prices in the following sections.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data for etelcalcetide comes from two phase 3, randomised, placebo controlled trials (Study 20120229 and Study 20120230), and a phase 3, randomised, active controlled trial (Study 20120360) presented in the main evidence submission (see section 4.7.1 and 4.7.2). In the base case analysis, outcomes data for use in the economic evaluation are derived by extrapolating to the EVOLVE calcimimetic outcomes trial as discussed in section 5.2.6 of the main submission. These analysis underpin the economic model and are not impacted by the implementation of the scheme.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence

There will be no costs associated with the implementation and operation of the proposed PAS as this scheme involves a simple confidential discount of [redacted] applied at the point of order.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Implementation of the PAS will not incur additional treatment-related costs.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

The cost-effectiveness of etelcalcetide is evaluated in two pair-wise comparisons:

- Established clinical practice without calcimimetics; PB/VD in patients with SHPT with chronic kidney disease, receiving haemodialysis (licensed indication)
- Cinacalcet in patients with refractory SHPT

These are in line with the decision problem outlined in the NICE scope (see section 1.2 of the main submission) and the treatment pathway described in section 3 of the main submission.

The base case cost-effectiveness results in the broad licensed indication comparing etelcalcetide (plus PB/VD) with PB/VD regimens alone with the list and PAS price for etelcalcetide are presented in Table 3 and Table 4, respectively.

The base case cost-effectiveness in patients with refractory SHPT comparing etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) with the list and PAS price for etelcalcetide are presented in Table 5 and Table 6, respectively.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3: Base case cost-effectiveness results etelcalcetide versus PB/VD – etelcalcetide list price

	Etelcalcetide*	PB/VD
Intervention cost (£)		
Calcimimetic	[redacted]	[redacted]
Phosphate Binders	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	6.423	5.985
LYG difference	NA	0.438
QALYs	4.109	3.788
QALY difference	NA	0.321
ICER (£)	NA	[redacted]

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

Table 4: Base case cost-effectiveness results etelcalcetide versus PB/VD – etelcalcetide PAS price

	Etelcalcetide*	PB/VD
Intervention cost (£)		
Calcimimetic	[redacted]	[redacted]
Phosphate Binders	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	£8,738
LYG	6.423	5.985
LYG difference	NA	0.438
QALYs	4.109	3.788
QALY difference	NA	0.321
ICER (£)	NA	£27,251

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

Table 5: Base case cost-effectiveness results etelcalcetide versus cinacalcet – etelcalcetide list price

	Etelcalcetide*	Cinacalcet*
Intervention cost (£)		
Calcimimetic	[redacted]	[redacted]
Phosphate Binders	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	[redacted]
LYG	6.423	6.329
LYG difference	NA	0.094
QALYs	4.109	4.888
QALY difference	NA	0.069
ICER (£)	NA	[redacted]

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

Table 6: Base case cost-effectiveness results etelcalcetide versus cinacalcet – etelcalcetide PAS price

	Etelcalcetide*	Cinacalcet*
Intervention cost (£)		
Calcimimetic	[redacted]	[redacted]
Phosphate Binders	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	NA	£1,020
LYG	6.423	6.329
LYG difference	NA	0.094
QALYs	4.109	4.888
QALY difference	NA	0.069
ICER (£)	NA	£14,778

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

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

The base incremental case cost-effectiveness results in the broad licensed indication comparing etelcalcetide (plus PB/VD) with PB/VD regimens alone with the list and PAS price for etelcalcetide are presented in Table 7 and Table 8, respectively.

The base incremental case cost-effectiveness in patients with refractory SHPT comparing etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) with the list and PAS price for etelcalcetide are presented in Table 9 and Table 10, respectively.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 7: Base case incremental results Etelcalcetide versus PB/VD – etelcalcetide list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PB/VD	[redacted]	5.985	3.788					
Etelcalcetide*	[redacted]	6.423	4.109	[redacted]	0.438	0.321	[redacted]	[redacted]

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

Table 8: Base case incremental results Etelcalcetide versus PB/VD – etelcalcetide PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PB/VD	[redacted]	5.985	3.788					
Etelcalcetide*	[redacted]	6.423	4.109	£8,738	0.438	0.321	£27,251	£27,251

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

Table 9: Base case incremental results Etelcalcetide versus cinacalcet – etelcalcetide list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cinacalcet*	[redacted]	6.329	4.888					
Etelcalcetide*	[redacted]	6.423	4.109	[redacted]	0.094	0.069	[redacted]	[redacted]
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD								

Table 10: Base case incremental results Etelcalcetide versus cinacalcet – etelcalcetide PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Cinacalcet*	[redacted]	6.329	4.888					
Etelcalcetide*	[redacted]	6.423	4.109	£1,020	0.094	0.069	£14,778	£14,778
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD								

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analyses results in the broad licensed indication comparing etelcalcetide (plus PB/VD) with PB/VD regimens alone with the list and PAS price for etelcalcetide are presented in Table 11 and Table 12, respectively. Tornado diagrams have also been presented with the list and PAS price in Figure 1 and Figure 2, respectively.

Deterministic sensitivity analyses results in patients with refractory SHPT comparing etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) with the list and PAS price for etelcalcetide are presented in Table 13 and Table 14, respectively. Tornado diagrams have also been presented with the list and PAS price in Figure 3 and Figure 4, respectively.

Table 11: Summary of univariate sensitivity analyses of etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide list price

Parameter	ICER low Input	ICER high Input
HR mort. (vs. PB/VD)	[redacted]	[redacted]
HR CV (vs. PB/VD)	[redacted]	[redacted]
HR Fx (vs. PB/VD)	[redacted]	[redacted]
HR PTx (vs. PB/VD)	[redacted]	[redacted]
Mortality rate	[redacted]	[redacted]
CV rate	[redacted]	[redacted]
Fracture rate	[redacted]	[redacted]
PTx rate	[redacted]	[redacted]
Utility dialysis	[redacted]	[redacted]
Utility decrements	[redacted]	[redacted]
Vitamin D + PB usage	[redacted]	[redacted]
Etelcalcetide dose	[redacted]	[redacted]
Event costs	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
Rate further CV event	[redacted]	[redacted]
Rate re-fracture	[redacted]	[redacted]
Persistence	[redacted]	[redacted]

CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RR, relative risk; PB, phosphate binder; PTx, parathyroidectomy; VD, vitamin D.

Figure 1: Tornado diagram on the ICER for etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide list price

Table 12: Summary of univariate sensitivity analyses of etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide PAS price

Parameter	ICER low Input	ICER high Input
HR mort. (vs. PB/VD)	20,467	47,245
HR CV (vs. PB/VD)	25,166	29,884
HR Fx (vs. PB/VD)	25,887	28,649
HR PTx (vs. PB/VD)	27,320	27,176
Mortality rate	26,835	27,667
CV rate	28,226	26,363
Fracture rate	27,398	27,095
PTx rate	27,314	27,191
Utility dialysis	27,042	27,453
Utility decrements	27,291	27,202
Vitamin D + PB usage	27,140	27,416
Etelcalcetide dose	26,138	28,855
Event costs	27,218	27,284
Monitoring costs	28,306	26,483
Rate further CV event	27,418	27,086
Rate re-fracture	27,635	26,867
Persistence	27,264	27,245

CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RR, relative risk; PB, phosphate binder; PTx, parathyroidectomy; VD, vitamin D.

Figure 2: Tornado diagram on the ICER for etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide PAS price

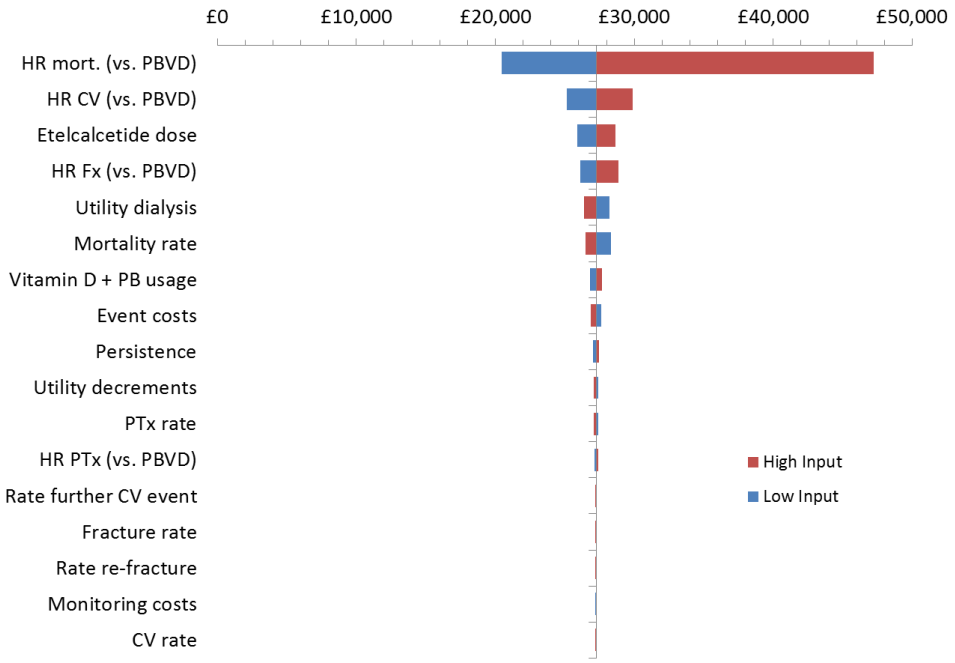


Table 13: Summary of univariate sensitivity analyses of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide list price

Parameter	ICER low Input	ICER high Input
HR mort. (vs. cina)	[redacted]	[redacted]
HR CV (vs. cina)	[redacted]	[redacted]
HR Fx (vs. cina)	[redacted]	[redacted]
HR PTx (vs. cina)	[redacted]	[redacted]
Mortality rate	[redacted]	[redacted]
CV rate	[redacted]	[redacted]
Fracture rate	[redacted]	[redacted]
PTx rate	[redacted]	[redacted]
Utility dialysis	[redacted]	[redacted]
Utility decrements	[redacted]	[redacted]
Vitamin D + PB usage	[redacted]	[redacted]
Etelcalcetide dose	[redacted]	[redacted]
Event costs	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
Rate further CV event	[redacted]	[redacted]
Rate re-fracture	[redacted]	[redacted]
Persistence	[redacted]	[redacted]

CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RR, relative risk; PB, phosphate binder; PTx, parathyroidectomy; VD, vitamin D.

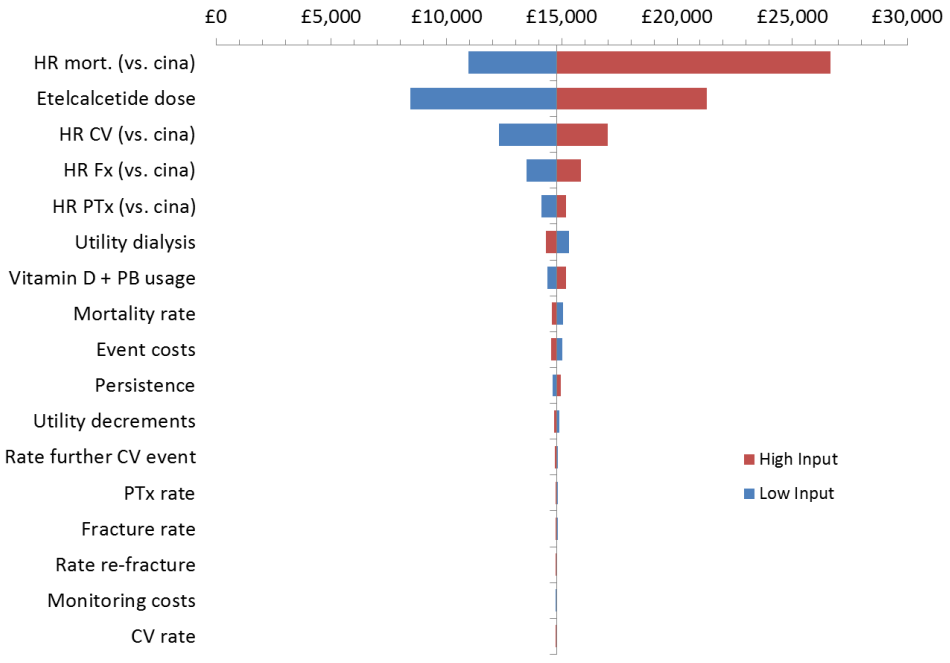
Figure 3: Tornado diagram on the ICER for etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide list price

Table 14: Summary of univariate sensitivity analyses of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide PAS price

Parameter	ICER low Input	ICER high Input
HR mort. (vs. cina)	10,959	26,647
HR CV (vs. cina)	12,266	17,000
HR Fx (vs. cina)	13,477	15,819
HR PTx (vs. cina)	14,745	14,811
Mortality rate	14,364	15,192
CV rate	15,305	14,298
Fracture rate	14,835	14,717
PTx rate	14,880	14,678
Utility dialysis	14,113	15,171
Utility decrements	14,593	14,966
Vitamin D + PB usage	14,810	14,739
Etelcalcetide dose	8,440	21,278
Event costs	14,821	14,736
Monitoring costs	15,009	14,547
Rate further CV event	14,842	14,709
Rate re-fracture	15,061	14,581
Persistence	14,804	14,756

CV, cardiovascular; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RR, relative risk; PB, phosphate binder; PTx, parathyroidectomy; VD, vitamin D.

Figure 4: Tornado diagram on the ICER for etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide PAS price



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis results in the broad licensed indication comparing etelcalcetide (plus PB/VD) with PB/VD regimens alone with the list and PAS price for etelcalcetide are presented in Table 15 and Table 16, respectively. Scatter plots are presented in Figure 5 and Figure 6, and cost-effectiveness acceptability curves are presented in Figure 7 and Figure 8.

Table 15: Mean probabilistic results of etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide list price

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
PB/VD	[redacted]	-	3.791 (0.087)	-	-
Etelcalcetide*	[redacted]	[redacted]	4.115 (0.123)	0.324 (0.083)	[redacted]

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

Table 16: Mean probabilistic results of etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide PAS price

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
PB/VD	[redacted]	-	3.791 (0.087)	-	-
Etelcalcetide*	[redacted]	8,791 (0,644)	4.115 (0.123)	0.324 (0.083)	27,133

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

Figure 5: Scatter plot of incremental QALYs vs. incremental costs of etelcalcetide (plus PBVD) vs. PB/VD – etelcalcetide list price

[redacted]

Figure 6: Scatter plot of incremental QALYs vs. incremental costs of etelcalcetide (plus PBVD) vs. PB/VD – etelcalcetide PAS price

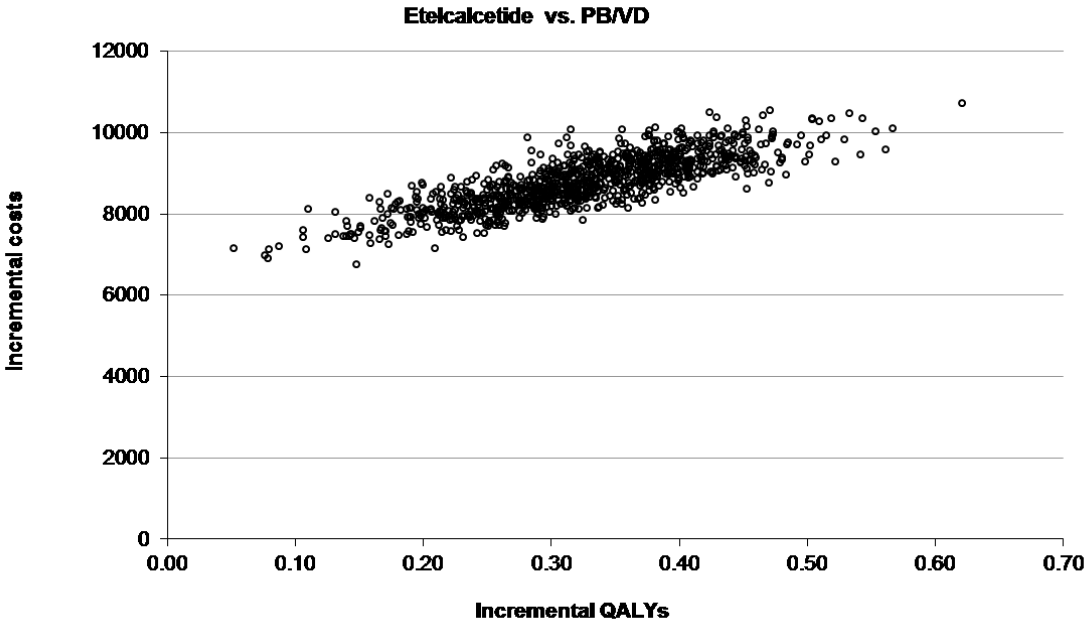
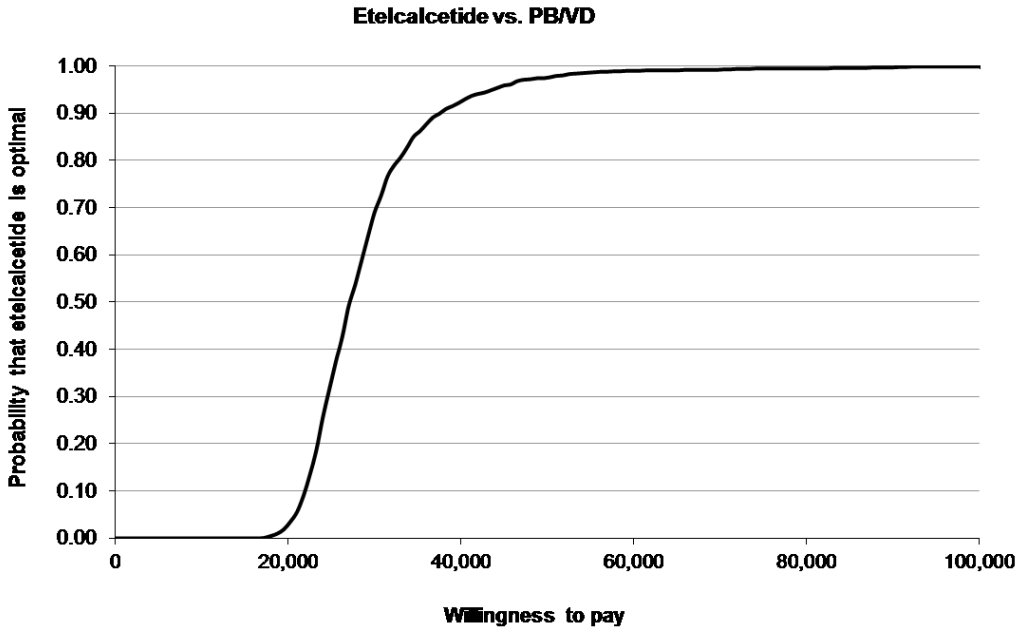


Figure 7: Cost-effectiveness acceptability curve for etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide list price

[redacted]

Figure 8: Cost-effectiveness acceptability curve for etelcalcetide (plus PB/VD) vs. PB/VD – etelcalcetide PAS price



Probabilistic sensitivity analysis results in patients with refractory SHPT comparing etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) with the list and PAS price for etelcalcetide are presented in Table 17 and Table 18, respectively. Scatter plots are presented in Figure 9 and Figure 10 and cost-effectiveness acceptability curves are presented in Figure 11 and Figure 12.

Table 17: Mean probabilistic results of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide list price

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Cinacalcet*	[redacted]	-	4.046 (0.111)	-	-
Etelcalcetide*	[redacted]	[redacted]	4.115 (0.123)	0.069 (0.024)	[redacted]

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

Table 18: Mean probabilistic results of etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide PAS price

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Cinacalcet*	[redacted]	-	4.046 (0.111)	-	-
[redacted]	[redacted]	1.039	4.115	0.069	

Figure 9: Scatter plot of incremental QALYs vs. incremental costs of etelcalcetide (plus PBVD) vs. cinacalcet (plus PB/VD) – etelcalcetide list price

Figure 10: Scatter plot of incremental QALYs vs. incremental costs of etelcalcetide (plus PBVD) vs. cinacalcet (plus PB/VD) – etelcalcetide PAS price

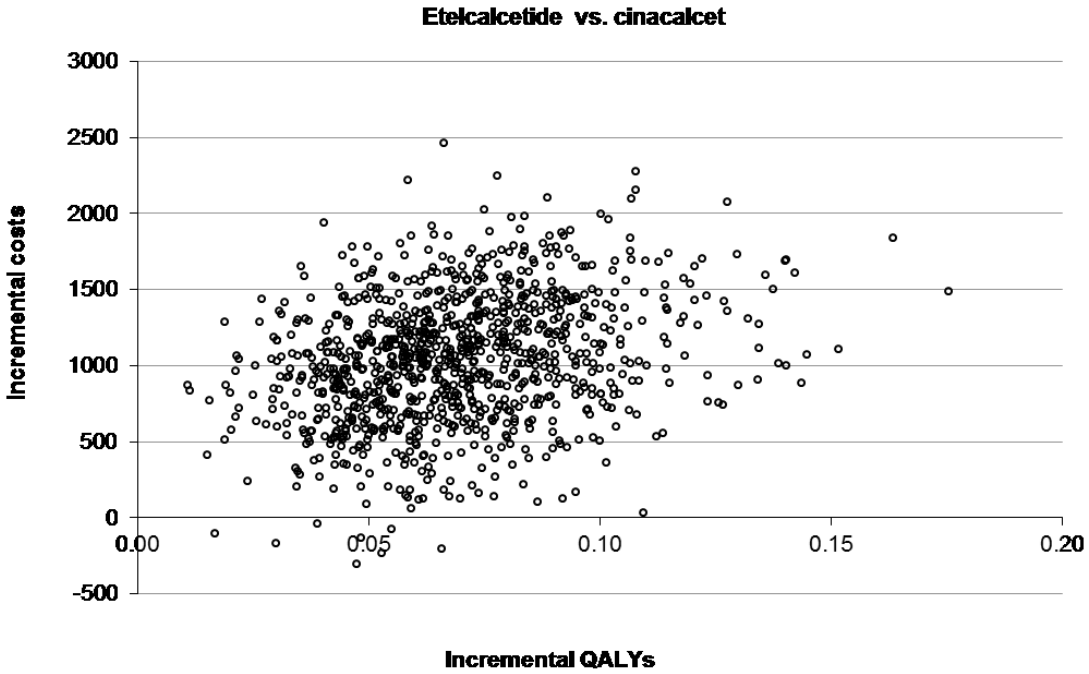
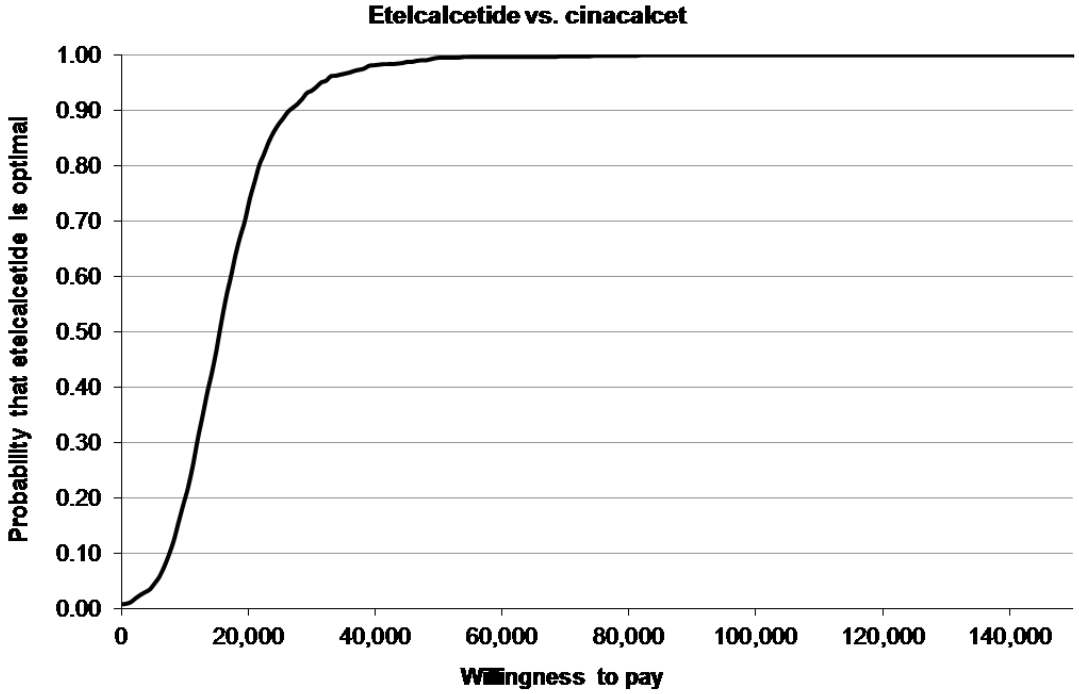


Figure 11: Cost-effectiveness acceptability curve for etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide list price

[redacted]

Figure 12: Cost-effectiveness acceptability curve for etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD) – etelcalcetide PAS price



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

A description of the key scenario analysis for the comparison of etelcalcetide (plus PB/VD) with PB/VD regimens alone is presented in the main submission of evidence (see section 5.2.5 and section 5.5.5); the resulting ICERs with the etelcalcetide list price and PAS price are presented in Table 19 and Table 20, respectively.

Table 19: Etelcalcetide (plus PB/VD) versus PB/VD alone – results of scenario analyses with etelcalcetide list price

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.321	[redacted]
Efficacy: EVOLVE ITT disaggregated	[redacted]	0.346	[redacted]
Efficacy: Eandi; censored	[redacted]	0.247	[redacted]
Efficacy: Eandi; ITT disaggregated	[redacted]	0.292	[redacted]
Age at baseline: 45 years	[redacted]	0.317	[redacted]
Age at baseline: 65 years	[redacted]	0.316	[redacted]
PTx: not included (rate=0)	[redacted]	0.320	[redacted]
Mortality: EVOLVE	[redacted]	0.310	[redacted]
Discontinuation: Reams et al	[redacted]	0.145	[redacted]
Discontinuation: Urena et al.	[redacted]	0.358	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER
Utility: Impact calcimimetic treatment	[redacted]	0.366	[redacted]
Calcimimetic drug use: EAP; head to head	[redacted]	0.321	[redacted]
Dialysis costs: included	[redacted]	0.321	[redacted]
Discount rate: 0%	[redacted]	0.412	[redacted]
Discount rate: 6%	[redacted]	0.274	[redacted]

Table 20: Etelcalcetide versus PB/VD alone – results of scenario analyses with etelcalcetide PAS price

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	8,738	0.321	27,251
Efficacy: EVOLVE ITT disaggregated	8,805	0.346	25,453
Efficacy: Eandi; censored	9,102	0.247	36,835
Efficacy: Eandi; ITT disaggregated	9,302	0.292	31,857
Age at baseline: 45 years	9,118	0.317	28,759
Age at baseline: 65 years	8,275	0.316	26,160
PTx: not included (rate=0)	9,122	0.320	28,525
Mortality: EVOLVE	8,532	0.310	27,490
Discontinuation: Reams et al	3,640	0.145	25,144
Discontinuation: Urena et al.	9,872	0.358	27,593
Utility: Impact calcimimetic treatment	8,738	0.366	23,843
Calcimimetic drug use: EAP; head to head	9,159	0.321	28,564
Dialysis costs: included	19,650	0.321	61,280
Discount rate: 0%	9,733	0.412	23,609
Discount rate: 6%	8,182	0.274	29,835

A description of the key scenario analysis for the comparison of etelcalcetide (plus PB/VD) with cinacalcet (plus PB/VD) is presented in the main submission of evidence (see section 5.2.5 and section 5.5.5); the resulting ICERs with the etelcalcetide list price and PAS price are presented in Table 21 and Table 22, respectively.

Table 21: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of scenario analyses with etelcalcetide list price

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.069	[redacted]
Efficacy: EVOLVE ITT disaggregated	[redacted]	0.074	[redacted]
Efficacy: Eandi; censored	[redacted]	0.057	[redacted]
Efficacy: Eandi; ITT disaggregated	[redacted]	0.074	[redacted]
Age at baseline: 45 years	[redacted]	0.067	[redacted]
Age at baseline: 65 years	[redacted]	0.316	[redacted]
PTx: not included (rate=0)	[redacted]	0.069	[redacted]
Mortality: EVOLVE	[redacted]	0.067	[redacted]
Discontinuation: Reams et al	[redacted]	0.031	[redacted]
Discontinuation: Urena et al.	[redacted]	0.078	[redacted]
Utility: Impact calcimimetic treatment	[redacted]	0.070	[redacted]
Calcimimetic drug use: EAP; head to head	[redacted]	0.069	[redacted]
Dialysis costs: included	[redacted]	0.069	[redacted]
Discount rate: 0%	[redacted]	0.089	[redacted]
Discount rate: 6%	[redacted]	0.059	[redacted]

Table 22: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of scenario analyses with etelcalcetide PAS price

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	1,020	0.069	14,778
Efficacy: EVOLVE ITT disaggregated	1,082	0.074	14,623
Efficacy: Eandi; censored	1,107	0.057	19,334
Efficacy: Eandi; ITT disaggregated	1,180	0.074	15,975
Age at baseline: 45 years	1,026	0.067	15,201
Age at baseline: 65 years	0,999	0.069	14,505
PTx: not included (rate=0)	1,053	0.069	15,272
Mortality: EVOLVE	1,002	0.067	14,963
Discontinuation: Reams et al	0,422	0.031	13,708
Discontinuation: Urena et al.	1,168	0.078	15,054
Utility: Impact calcimimetic treatment	1,020	0.070	14,634
Calcimimetic drug use: EAP; head to head	1,441	0.069	20,880
Dialysis costs: included	3,358	0.069	48,678
Discount rate: 0%	1,173	0.089	13,157
Discount rate: 6%	0,937	0.059	15,938

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

The cost-effectiveness results for the base case and scenario analyses with and without the proposed etelcalcetide PAS are provided in Table 17 for etelcalcetide (plus PB/VD) versus PB/VD alone and in Table 18 for etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD).

Table 23: Etelcalcetide (plus PB/VD) versus PB/VD alone – impact of PAS on ICERs

Scenario	ICER without PAS, £ per QALY	ICER with PAS, £ per QALY
Base case	[redacted]	27,251
Efficacy: EVOLVE ITT disaggregated	[redacted]	25,453
Efficacy: Eandi; censored	[redacted]	36,835
Efficacy: Eandi; ITT disaggregated	[redacted]	31,857
Age at baseline: 45 years	[redacted]	28,759
Age at baseline: 65 years	[redacted]	26,160
PTx: not included (rate=0)	[redacted]	28,525
Mortality: EVOLVE	[redacted]	27,490
Discontinuation: Reams et al	[redacted]	25,144
Discontinuation: Urena et al.	[redacted]	27,593
Utility: Impact calcimimetic treatment	[redacted]	23,843
Calcimimetic drug use: EAP; head to head	[redacted]	28,564
Dialysis costs: included	[redacted]	61,280
Discount rate: 0%	[redacted]	23,609
Discount rate: 6%	[redacted]	29,835

Table 24: Etelcalcetide (plus PB/VD) versus cinacalcet plus (PB/VD) – impact of PAS on ICERs

Scenario	ICER without PAS, £ per QALY	ICER with PAS, £ per QALY
Base case	[redacted]	14,778
Efficacy: EVOLVE ITT disaggregated	[redacted]	14,623
Efficacy: Eandi; censored	[redacted]	19,334
Efficacy: Eandi; ITT disaggregated	[redacted]	15,975
Age at baseline: 45 years	[redacted]	15,201
Age at baseline: 65 years	[redacted]	14,505
PTx: not included (rate=0)	[redacted]	15,272
Mortality: EVOLVE	[redacted]	14,963
Discontinuation: Reams et al	[redacted]	13,708
Discontinuation: Urena et al.	[redacted]	15,054
Utility: Impact calcimimetic treatment	[redacted]	14,634
Calcimimetic drug use: EAP; head to head	[redacted]	20,880
Dialysis costs: included	[redacted]	48,678
Discount rate: 0%	[redacted]	13,157
Discount rate: 6%	[redacted]	15,938

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the

patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not applicable.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

Dear Kawitha,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 26 October 2016 from Amgen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **2 December 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals **https://appraisals.nice.org.uk/request/21285**

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted] Technical Lead [redacted] . Any procedural questions should be addressed to [redacted], Project Manager TACommA@nice.org.uk .

Yours sincerely

Joanna Richardson
Technical Advisor – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Study selection

A1. Please explain how the 5 non-RCT studies listed in table 20 of the company submission (page 70) were identified and screened for inclusion in the submission? For example, were they identified through the searches for the systematic literature review or from the company's records? What criteria were used to determine the relevance of these studies for inclusion in the submission?

Treatment in the trials

A2. In trials 20120229, 20120230 and 20120360, all participants received background therapy which could include calcium supplements, vitamin D sterols, nutritional vitamin D and phosphate binders. Please clarify whether background therapy also included dietary modification to reduce phosphate intake and/or changes to the dialysis regimen, as needed?

Discontinuations in the trials

A3. Table 13 of the company submission shows the number of patients in each arm of studies 20120229, 20120230 and 20120360 who discontinued treatment due to 'decision by sponsor'. Please clarify on what basis these decisions were made.

Trials' methodology and statistical analyses

A4. Please provide further information about how double blinding was preserved in trials 20120229 and 20120230. For instance, table 10 in the company submission states in studies 20120229, 20120230 and 20120360 the etelcalcetide dose could be titrated every 4 weeks on the basis of parathyroid hormone (PTH) and corrected calcium concentrations (cCa). Did patients in the placebo arms in studies 20120229 and 20120230 and the cinacalcet arm in study 20120360 undergo similar procedures to measure PTH and cCa concentrations to patients in the etelcalcetide arms to preserve blinding? Furthermore, who made decisions to titrate the dose and were they blind to treatment allocation?

A5. Page 50 of the company submission states that "the non-inferiority null method" was used to impute missing data in study 20120360. Please clarify what this method involves.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A6. [redacted]. Please confirm if this is correct.

A7. **Priority question:** Page 68 of the company submission provides the results of post-hoc analyses of outcomes among a sub-group patients in the placebo-controlled studies 20120229 and 20120230 who [redacted]. Please provide the results of similar post-hoc analyses of outcomes among this patient subgroup in the active-controlled (cinacalcet-controlled) study 20120360.

A8. Was there any patient crossover in the RCTs included in the submission (20120229, 20120230 and 20120360). If so, did the analyses take into account patient crossover?

Follow-up studies

A9. How many patients from the respective arms of the 20120229 and 20120230 RCTs were included in the 20130213 (OLE1) open-label extension study? What were the criteria for these patients to enter into this study? Likewise, how many patients from the respective arms of the 20120360 RCT entered into open-label extension study 20130213 (OLE2)? What were the criteria for these patients to enter into this study? When will the final results of 20130213 (OLE2) be available?

Data synthesis

A10. **Priority question:** Page 38 of the company submission states [redacted]
Page 69 of the submission states indirect and mixed treatment comparisons were not undertaken as direct comparative data for etelcalcetide and the comparators were available. Given the original intention was to [redacted], please provide more details about the decision not to do an NMA, based on the results of the feasibility assessment. Please also clarify how many studies comparing cinacalcet versus placebo and/or standard of care were identified from the searches and inclusion screening process that measured 'achievement of a > 30% reduction in mean PTH from baseline during the efficacy assessment phase' as an outcome. Please provide a reference list of these studies.

Health-related quality of life results in trial 20120360

A11. **Priority question:** Table 11 (company submission, page 47) states health-related quality of life (HRQoL) was measured in study 20120360 using the KDQOL-36

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

(Kidney Disease Quality of Life questionnaire), but results for this outcome have not been provided in the main submission. The ERG located these results in the Clinical Study Report, but no interpretation of the meaning of the results is provided. Please provide some discussion of what the results mean and guidance on how to interpret the [redacted]. For example, is a higher or lower score indicative of better quality of life? Is the [redacted] a composite of the mean scores on each of the four subscales of this measure? Please also provide a citation for the KDQOL-36, and details of its validation.

Section B: Clarification on cost-effectiveness data

Adjustments for non-adherence

B1. It is stated on page 96 of the company submission that the lag-censored analysis was pre-specified to adjust for non-adherence in EVOLVE. However, the paper by Kubo and colleagues (reference 38 in the submission) suggests that four methods of accounting for non-adherence were all planned as sensitivity analysis: lag censoring; inverse probability of censoring weights (IPCW); rank preserving structural failure time model (RPSFTM) and iterative parameter estimation (IPE). Please clarify whether any of these methods was preferred a priori. If so, please explain why.

B2. **Priority question:** It is noted on page 97 of the company submission that some challenges were experienced in applying methods suggested in NICE Decision Support Unit technical support document 16 to adjust for non-adherence in EVOLVE outcomes needed for the economic model. In particular, it is noted that the IPCW method could not be applied to fracture and parathyroidectomy (PTx) endpoints due to the small number of events. This suggests that this method was applied to the other endpoints of interest: all-cause mortality and non-fatal CV events. It is also noted that the RPSFTM and IPE methods do not have the same data requirements. Please provide results (hazard ratios with confidence intervals) for IPCW, RPSFTM and IPE methods applied to all individual event types (all-cause mortality, fracture, non-fatal cardiovascular events and PTx) that could be evaluated. Please also provide further justification as to why the RPSFTM and IPE methods were considered not to be the most appropriate.

B3. **Priority question:** Sensitivity analysis of the duration of lag assumed in the lag-censored analysis for EVOLVE is presented for the primary composite outcome in EVOLVE (Table S7, p45 Chertow et al NEJM 2012, supplementary appendix). Please present this same analysis for the individual model endpoints (all-cause survival, non-fatal cardiovascular events, fractures and PTx).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Extrapolation of etelcalcetide trial data

B4. **Priority question:** It is noted on page 101 of the submission that the rationale for the surrogate endpoint used for the extrapolation in the Section 5.2.6.3 is that it was the primary outcome for the etelcalcetide trials (>30% reduction in PTH from baseline). However, it is likely that absolute control of PTH levels (e.g. achievement of mean PTH within ≤ 300 pg/ml during the efficacy assessment phase) would be a better predictor of the incidence of long-term clinical outcomes (mortality, cardiovascular events, fractures and PTx) rather than a percentage change. Please conduct a scenario analysis to test the sensitivity of the estimated hazard ratios and ICERs to extrapolation of the etelcalcetide trials to EVOLVE endpoints using an absolute measure of PTH control (achievement of PTH target range).

Discontinuation rates

B5. **Priority question:** Please provide one-year discontinuation rates for cinacalcet from the EVOLVE trial by region (USA, Europe, and other regions).

B6. **Priority question:** Please provide time to discontinuation data, if available, for the open-label extension studies 20120231 and 20120213.

Other

B7. **Priority question:** Please provide the absolute event rates (number of events and number of patients) for the cinacalcet and placebo arms for each of the pre-defined 'region' and 'PTH group' subgroups in the EVOLVE trial (as shown in Figure S2, p. 11 of Chertow et al. NEJM 2012 supplementary appendix) for the following outcomes: all-cause mortality, the non-fatal cardiovascular event composite (myocardial infarction, hospitalisation for unstable angina, heart failure, peripheral vascular event), stroke, non-fatal fractures and PTx.

B8. Please clarify whether intravenous administration of etelcalcetide would incur additional costs to the NHS: more nurse time and/or increased duration of the haemodialysis session.

<u>Section C: Textual clarifications and additional points</u>

C1. Please provide the full clinical study report for study 20120231 (reference 32 in the submission; only a synopsis was provided with the original submission) and Amgen data on file for study 20120213 (reference 33, 'interim analysis summary').

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

C2. **Priority question:** The EVOLVE trial is a key data source for estimated clinical effects in the de novo economic evaluation in chapter 5 of the company submission. Please provide a copy of the Clinical Study Report for this trial.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Etelcalcetide for the treatment of secondary hyperparathyroidism [ID908]

Response to clarification questions

Prepared by:

Date: December 2016

File name	Version	Contains confidential information	Date
Etelcalcetide_ID908_Response to clarification questions_17th Feb 2017_redacted	1.1	Redacted	17th February 2017

Contents

List of tables

List of figures

Introduction

Thank you for the opportunity to respond to questions from the Evidence Review Group (ERG) and to clarify key aspects of the evidence submission for etelcalcetide [ID908]. Detailed responses to the ERG questions are provided in:

- Section A (clarification on clinical effectiveness data);
- Section B (clarification on cost-effectiveness data); and
- Section C (textual clarification and additional points).

We would like to take this opportunity to re-iterate that the cost-effectiveness analyses presented in this response are based on the list price of etelcalcetide. Amgen has proposed a patient access scheme (PAS) to the Department of Health, which is under consideration by the PAS Liaison Unit.

A: Clarification on clinical-effectiveness data

Study selection

A1. Please explain how the 5 non-RCT studies listed in table 20 of the company submission (page 70) were identified and screened for inclusion in the submission? For example, were they identified through the searches for the systematic literature review or from the company's records? What criteria were used to determine the relevance of these studies for inclusion in the submission?

The non-randomised trials of etelcalcetide reported in the clinical development programme and supporting the marketing authorisation application to the EMA (CHMP assessment report, 2016) were identified from company records (see section 4.1.1 of our original submission). These included:

i. a single arm, phase 3 switch study (20120359) (n=158)

ii. a phase 3 open-label extension study (20120231) that enrolled patients from the two placebo-controlled phase 3 trials and the single-arm switch study (n=891)

iii. a further phase 3 open-label extension study (20130213) that enrolled patients from the open-label study 20120231, the phase 3 active controlled trial, and the phase 2 open-label extensions study 20120334 (n=902 from most recent interim analysis)

iv. a small, single-arm dose titration study (20120331) that explored dosing up to 20mg three times per week (n=37)

v. a phase 2 open-label extension of the small dose titration study (20120334) (n=30, terminated early, with patients rolling over into the phase 3 open-label extension study 20130213).

Studies 20120231 and 20130213 provide long-term data on the safety and efficacy of etelcalcetide at licensed doses and as used in clinical practice, in large numbers of patients. Study 20120359 provides data on the safety and efficacy of etelcalcetide when switching from cinacalcet at the dosing schedule recommended in practice, in large numbers of patients. These studies were therefore considered to provide highly relevant evidence that could usefully help to address the decision problem outlined in the NICE scope.

In contrast, study 20120331 was essentially a dose-response study conducted in a small number of patients (n=37), which permitted dose titration beyond the licensed maximum dose of etelcalcetide. Whilst informing the dose-response relationship and final dosing recommendations for regulatory purposes, this study was not considered to provide data of the same relevance to the decision problem outlined in the NICE scope. For this reason the study was noted but not further discussed in our submission. (Results of the study 20120331 are included in the draft CHMP assessment report that was provided as a reference).

Study 20120334 was an open-label extension to this dose-response study, intended to run for an initial 40 weeks, followed by extension up to 2 years. Thirty patients were enrolled from 20120331 but the study was terminated early, and patients were rolled over into the phase 3 study 20130213. Therefore, as with its parent study, study 20120344 was noted but not further discussed in our submission.

In summary, the five non-randomised studies referred to in our submission reflect the available non-randomised clinical data in the etelcalcetide clinical development programme. Three of these studies provide data that are highly relevant to the efficacy and safety of etelcalcetide when used as anticipated in clinical practice, and were discussed in detail in our submission to NICE; the remaining two non-randomised studies were noted for completeness but not further discussed on the basis of their limited relevance and limited ability to further inform the comprehensive, consistent and highly relevant evidence base for etelcalcetide available from three large phase 3 RCTs, two large open-label extension studies and the large single-arm switch study.

References:

European Medicines Agency. CHMP Assessment Report: Parsabiv 2016.

Treatment in the trials

A2. In trials 20120229, 20120230 and 20120360, all participants received background therapy which could include calcium supplements, vitamin D sterols, nutritional vitamin D and phosphate binders. Please clarify whether background therapy also included dietary modification to reduce phosphate intake and/or changes to the dialysis regimen, as needed?

In all three RCTs (20120229, 20120230, and 20120360), background therapy included dietary modification to reduce phosphate intake and changes in dialysate to help control calcium levels. As specified in study protocols, adjustment of background therapy was at the clinical discretion of the investigator based on the guidance that phosphate binder dose should be increased only if 2 consecutive local predialysis serum values were >5.5 mg/dL and not amenable to dietary counselling (guidance was also provided on reducing phosphate binder doses). Changes in the dialysate calcium concentration were permitted to help manage cases of hypocalcaemia and hypercalcaemia. If a subject had hypercalcaemia, then doses of active vitamin D sterol, oral calcium intake, and/or dialysate calcium concentration could be reduced based on Investigator clinical judgment; however, dialysate calcium concentration had to remain ≥ 2.25 mEq/L in the placebo controlled RCTs and >2.5 mEq/L in the active-controlled RCT.

References:

Amgen. A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis. Amgen Protocol Number: 20120229 (also known as KAI-4169-006); 2013.

Amgen. A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis. Amgen Protocol Number: 20120230 (also known as KAI-4169-007); 2013.

Amgen. A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism (also known as KAI-4169). Amgen Protocol Number 20120360; 2014.

Discontinuations in the trials

A3. Table 13 of the company submission shows the number of patients in each arm of studies 20120229, 20120230 and 20120360 who discontinued treatment due to 'decision by sponsor'. Please clarify on what basis these decisions were made.

In the phase 3 trials, 'decision by sponsor' was included as a reason for discontinuation of patients from the protocol required investigational product alongside other possible reasons, including:

- subject request
- safety concern (eg, due to an adverse event, failure to follow contraception, breast feeding, and/or protocol requirements)
- subject requires a significant permanent change in haemodialysis prescription to maintain adequate haemodialysis
- subject receives a kidney transplant
- subject undergoes a parathyroidectomy
- death
- lost to follow-up.

As indicated in Table 1 below, 3 patients in study 20120229, 11 patients in study 20120230 and 2 patients in study 20120360 discontinued from treatment due to 'decision by sponsor'. Further detail behind the broad reasons for treatment discontinuation was not consistently recorded in the electronic case report forms; however, internal communications indicate that the 14 patients in the placebo-controlled trials who discontinued treatment due to 'decision by sponsor' did so due to relocation of patients to dialysis facilities that were not accredited for trial participation or due to site-specific issues, rather than patient issues. It is not possible to provide further detail behind the 2 patients in the active-controlled trial who discontinued treatment due to 'decision by sponsor'.

To put these figures into context, 'decision by sponsor' accounted for <5% of all reasons for treatment discontinuation across the three phase 3 trials, and patients who discontinued treatment due to 'decision by sponsor' accounted for <1% of all randomised patients across the three trials. There is no obvious difference in rates of discontinuations due to 'decision by sponsor' between the trial arms (8 in the etelcalcetide arms, and 8 in the trial comparator arms). It is therefore highly improbable that treatment discontinuations due to 'decision by sponsor' could have biased the results observed in the phase 3 trials.

Table 1: Frequency of 'Decision by sponsor' reason treatment discontinuation in the phase 3 etelcalcetide trials

	Study 20120229		Study 20120230		Study 20120360	
	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet	Etelcalcetide
Efficacy population, n	254	254	260	255	343	340
Discontinued from treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decision by sponsor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HD, haemodialysis; NA, not applicable; PTH, parathyroid hormone
Source: 20120229, 20120230, 20120360 clinical study reports

References:
Amgen. 20120229 Clinical Study Report. 2014.
Amgen. 20120230 Clinical Study Report. 2014.
Amgen. 20120360 Clinical Study Report. 2015.

Trial methodology and statistical analyses

A4. Please provide further information about how double blinding was preserved in trials 20120229 and 20120230. For instance, table 10 in the company submission states in studies 20120229, 20120230 and 20120360 the etelcalcetide dose could be titrated every 4 weeks on the basis of parathyroid hormone (PTH) and corrected calcium concentrations (cCa). Did patients in the placebo arms in studies 20120229 and 20120230 and the cinacalcet arm in study 20120360 undergo similar procedures to measure PTH and cCa concentrations to patients in the etelcalcetide arms to preserve blinding? Furthermore, who made decisions to titrate the dose and were they blind to treatment allocation?

In all three studies (20120229, 20120230, and 20120360) investigators and patients were blinded to treatment assignment. Investigators were blinded to serum PTH and phosphorus. cCa results were not blinded for safety reasons. Routine local PTH monitoring was suspended during the studies and investigational product dose titration (increase/decrease/maintenance) and dose suspension was managed by an interactive voice/web response system (IXRS) based on serum iPTH and cCa results obtained during the prior week. To maintain blinding, the IXRS also assigned dose titration and suspension to placebo patients to mimic patients in the etelcalcetide group.

Trial site personnel did not have access to a patient's individual treatment assignment unless the study was formally unblinded. A patient's treatment assignment could only be unblinded when knowledge of the treatment was essential for the further management of the patient on the study. Unblinding at the study site for any other reason was considered a protocol deviation.

The protocol included rules for the suspension of investigational product dosing for pre-dialysis serum cCa < 7.5 mg/dL, 2 consecutive pre-dialysis serum iPTH < 100 pg/mL, symptomatic hypocalcaemia, or other adverse events that necessitated withholding of investigational product. In cases where the Investigator elected to withhold investigational product because

of the occurrence of an adverse event that may be caused by or exacerbated by investigational product administration, the adverse event(s) (eg, abnormal ECG findings, nausea, hypocalcaemia) were to be managed by the Investigator by assuming that the patient was receiving active drug product without the need for unblinding to treatment allocation.

If the Investigator believed it was essential to break the blind in order to manage a patient's treatment, the procedures outlined in the Investigational Product Instruction Manual (IPIM) and IXRS manual were to be followed. Any unblinding was managed through the IXRS.

References:

Amgen. A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis. Amgen Protocol Number: 20120229 (also known as KAI-4169-006); 2013.

Amgen. A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis. Amgen Protocol Number: 20120230 (also known as KAI-4169-007); 2013.

Amgen. A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism (also known as KAI-4169). Amgen Protocol Number 20120360; 2014.

A5. Page 50 of the company submission states that "the non-inferiority null method" was used to impute missing data in study 20120360. Please clarify what this method involves.

For the primary (non-inferiority) analysis, multiple imputation under the non-inferiority null method (Koch 2008) was employed if patients had missing PTH data during the efficacy assessment phase. Under this imputation approach, a response rate of 60% was applied to impute response status in patients in the cinacalcet group with missing data, and a response rate of 48% was applied to impute response status in patients in the etelcalcetide group with missing data. The imputation was performed 5 times to account for variability introduced by imputation.

A 60% response rate for imputing missing response data for the cinacalcet group in study 20120360 was chosen based on the proportion of cinacalcet recipients with > 30% reduction in PTH from baseline in the first 6 months of the large placebo-controlled EVOLVE study. Study 20120360 pre-specified a 12% non-inferiority margin (Amgen 2014); hence, a 48% response rate was chosen as a conservative rate to impute missing response data for the etelcalcetide group.

Reference:

Koch GG. Comments on 'current issues in non-inferiority trials' by Thomas R. Fleming. Stat Med 2008; 27:333-342.

Amgen. A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism (also known as KAI-4169). Amgen Protocol Number 20120360; 2014.

A6. [redacted]. Please confirm if this is correct.

We can confirm that [redacted]

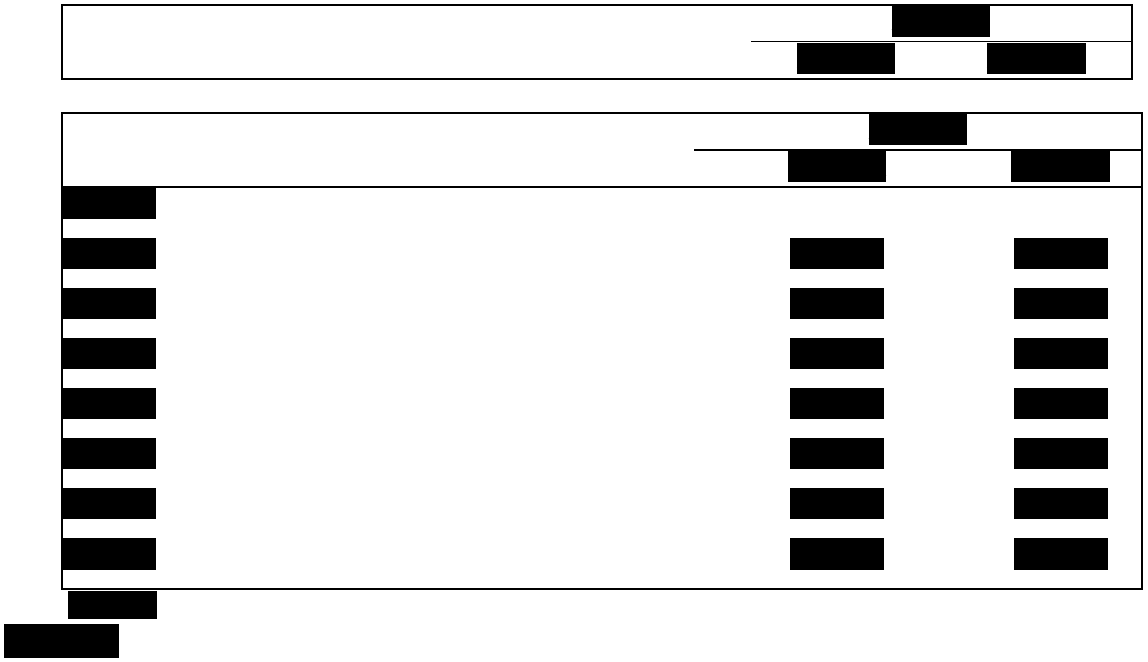
In relation to clarification question A7 below, we can confirm that the [redacted]

As noted in our submission and in response to clarification question A7 below, these are post hoc subgroup analyses in small numbers of patients – [redacted] We consider these data are aligned with the findings of the pre-specified subgroups presented in our submission, which indicate that etelcalcetide is effective across the broad spectrum of patients meeting its licensed indication; however, we acknowledge and advise that these data from post hoc analyses in very small patient numbers should be interpreted with caution. This is particularly so as cinacalcet is specified as a comparator in the final scope and is unlikely to represent a treatment option in practice for patients who have failed on prior cinacalcet therapy.

A7. <u>Priority question:</u> Page 68 of the company submission provides the results of post-hoc analyses of outcomes among a sub-group patients in the placebo-controlled studies 20120229 and 20120230 who [redacted]. Please provide the results of similar post-hoc analyses of outcomes among this patient subgroup in the active-controlled (cinacalcet-controlled) study 20120360.

As requested, we have conducted post hoc subgroup analyses of patients in the active-controlled study 20120360 who had discontinued cinacalcet due to either a lack of efficacy, or adverse reactions or intolerability (Amgen data on file, 2016). **However, as the final NICE scope includes cinacalcet as a comparator, and those patients who have failed cinacalcet are unlikely to be candidates for cinacalcet treatment in practice, we consider this analysis to be outwith the scope of the appraisal of etelcalcetide.**

[redacted]Table 2: [redacted]



References:

Amgen data on file. Etelcalcetide efficacy and safety in cinacalcet failure subgroup of study 20120360; November 2016.

A8. Was there any patient crossover in the RCTs included in the submission (20120229, 20120230 and 20120360)? If so, did the analyses take into account patient crossover?

Crossover from one treatment arm to another was not an option and the IXRS was not programmed to accommodate crossover. Therefore crossover was not assessed in the trials. Efficacy endpoints were analysed on the full analysis set (i.e. intention to treat basis), which would not have accounted for any patient crossover had this been possible. No other efficacy analyses were pre-specified in the trial protocols.

Follow-up studies

A9. How many patients from the respective arms of the 20120229 and 20120230 RCTs were included in the 20130213 (OLE1) open-label extension study? What were the criteria for these patients to enter into this study? Likewise, how many patients from the respective arms of the 20120360 RCT entered into open-label extension study 20130213 (OLE2)? What were the criteria for these patients to enter into this study? When will the final results of 20130213 (OLE2) be available?

Study 20120231:

A total of 891 patients were enrolled in study 20120231 (OLE1). Of these 768 were enrolled from the two placebo-controlled RCTs (384 patients from placebo and 384 from etelcalcetide arms). The remaining 123 patients were enrolled from the single-arm switch study (20120359). One patient from the placebo arm of study 20120229 was enrolled did not receive etelcalcetide in this extension study.

Criteria for enrolment of patients in 20120231 (OLE1) were completion of an etelcalcetide phase 3 parent study (20120229, 20120230, or 20120359) or discontinuation because of rising PTH from studies 20120229 or 20120230. Patients had dialysate calcium concentration ≥ 2.25 mEq/L. Patients were excluded if they had received cinacalcet between the last dose of investigational product in the parent study and the start of dosing in this study. Patients were also excluded if they had an unstable medical condition or a history or evidence of clinically significant disorder, condition, or disease that would pose a risk to their safety.

Study 20130213;

Based on the interim analysis 15 January 2015, study 20130213 (OLE2) enrolled 409 patients from study 20120360: 211 patients from the cinacalcet arm and 198 from the etelcalcetide arm. One patient enrolled from the etelcalcetide arm of study 20120360 did not subsequently receive etelcalcetide in the extension study. Five patients from each arm of study 20120360 did not receive etelcalcetide in this extension study.

Patients receiving haemodialysis 3 or 4 times weekly for at least 3 months and who had either completed treatment in study 20120231 (OLE1) or study 20120360 or had participated in study 20120334 were eligible for enrolment in study 20130213 (OLE2). Patients were excluded if they had received cinacalcet between the last dose of investigational product in the parent study and the start of dosing in this study.

Final results of study 20130213 are expected May 2017.

References:
Amgen. Clinical Study Report 20120231; 2015.
Amgen. Clinical Study Report 20130213 – Interim Analysis, January 2016.

Data synthesis

A10. Priority question: Page 38 of the company submission states [redacted]. Page 69 of the submission states indirect and mixed treatment comparisons were not undertaken as direct comparative data for etelcalcetide and the comparators were available. Given the original intention was to [redacted], please provide more details about the decision not to do an NMA, based on the results of the feasibility assessment. Please also clarify how many studies comparing cinacalcet versus placebo and/or standard of care were identified from the searches and inclusion screening process that measured 'achievement of a > 30% reduction in mean PTH from baseline during the efficacy assessment phase' as an outcome. Please provide a reference list of these studies.

For clarification, the SLR was conducted to enable Amgen to meet the needs of HTA bodies in jurisdictions across the world, including the UK. The SLR was initiated prior to the receipt of the final scope from NICE or any other HTA body, and was therefore conducted to identify all relevant RCTs providing clinical efficacy and safety data for etelcalcetide and other approved

treatments for SHPT, should indirect or mixed treatment comparisons of trials of SHPT treatments be required.

The final NICE scope for the appraisal of etelcalcetide specifies the relevant comparators as (NICE Final Scope; 2016):

- Established clinical practice without calcimimetics (dietary modification to restrict phosphate, phosphate binders, analogues of vitamin D), and
- Cinacalcet (for patients with refractory SHPT).

Robust, direct comparative data for etelcalcetide and these comparators are available from three large, phase 3 RCTs (studies 20120229, 20120230 and 20120360), as presented in our submission. As noted in the quality assessment of these trials in section 4.6 of our submission, these three RCTs have high internal validity and their results are at a low risk of bias. Due to the availability of this high quality, direct comparative evidence, and in line with section 5.1.2 of the 2013 *NICE Guide to the methods of technology appraisal* that states "The Institute has a preference for RCTs directly comparing the intervention with 1 or more relevant comparators and these should be presented in the reference-case analysis if available" (NICE 2013), indirect or mixed treatment comparisons were not necessary for this submission. A formal evidence synthesis feasibility assessment was therefore not undertaken for this submission. We therefore stated in section 4.10 of our submission that, as direct comparative data for etelcalcetide and the comparators listed in the final scope are available from high-quality, phase 3 RCTs, indirect and mixed treatment comparisons have not been undertaken for this submission.

In summary, the SLR was initiated using broader inclusion criteria than those required to identify relevant trials of etelcalcetide, should it have been necessary to consider conducting indirect or mixed treatment comparisons. This was not necessary for this submission. We apologise for any confusion arising from the summary description of our SLR in our original submission and confirm that this broad SLR was used only to confirm that we had identified all relevant RCTs of etelcalcetide. We are pleased to be able to provide NICE with the most robust and relevant evidence possible to address the decision problem outlined in the final scope for the appraisal of etelcalcetide, in line with the Institute's preferences, and without the need to rely on a NMA and the inherent assumptions and uncertainties that would entail.

As requested, and for your reference only, Table 3 lists the RCTs we identified from our literature searches that compared cinacalcet against placebo/standard of care that report 'achievement of a > 30% reduction in mean PTH from baseline during the efficacy assessment phase' as an outcome.

Table 3: RCTs of cinacalcet vs. placebo/standard of care reporting achievement of >30% reduction in mean PTH during efficacy assessment phase

Trial ID	Citation
Amgen 20000172	Amgen. A study of an investigational medication for the treatment of secondary hyperparathyroidism in dialysis patients. NCT00037635. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2003 [accessed 19.1.15]. Available from: http://ClinicalTrials.gov/show/NCT00037635
	Block GA, Martin KJ, Turner SA, Avram MM, Hercz G, Abu-Alfa AK, et al. Phase 3 study results demonstrate efficacy and safety of the calcimimetic cinacalcet HCl in hemodialysis patients with secondary hyperparathyroidism (HPT). Presented at 36th

Trial ID	Citation
	Annual Meeting American Society of Nephrology; 12-17 Nov 2003; San Diego, USA. *J Am Soc Nephrol* 2003;14:461A.
	Martin KJ, Juppner H, Sherrard DJ, Goodman WG, Kaplan MR, Nassar G, et al. First- and second-generation immunometric PTH assays during treatment of hyperparathyroidism with cinacalcet HCl. *Kidney Int* 2005;68(3):1236-43.
	Amgen. *A phase 3 study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of end stage renal disease treated with hemodialysis (Clinical Study Report: 20000172)* . Thousand Oaks, CA: Amgen, 2003. 9335p.
Amgen 20000183	Amgen. *A phase 3 study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of end stage renal disease treated with haemodialysis (Clinical Study Report: 20000183)* . Thousand Oaks, CA: Amgen, 2003. 6997p.
	Amgen. Safety and efficacy study of AMG 073 in hemodialysis subjects. NCT00527267. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 16.1.15]. Available from: http://ClinicalTrials.gov/show/NCT00527267
Amgen 20000188	Amgen. A study of an investigational medication for the treatment of secondary hyperparathyroidism in patients on dialysis. NCT00042653. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 19.1.15]. Available from: http://ClinicalTrials.gov/show/NCT00042653
	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):800-7.
	Amgen. *A placebo-controlled, double-blind, multicenter study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of chronic kidney disease (hemodialysis and peritoneal dialysis) (Clinical Study Report: 20000188)* . Thousand Oaks, CA: Amgen, 2003. 8522p.
Amgen 20010141	Amgen. 12-month Study of AMG 073 in Renal Osteodystrophy. 2013. Available from: http://ClinicalTrials.gov/show/NCT00527085
	Malluche HH, Monier-Faugere MC, Wang G, Frazao JM, Charytan C, Coburn JW, et al. An assessment of cinacalcet HCl effects on bone histology in dialysis patients with secondary hyperparathyroidism. *Clin Nephrol* 2008;69(4):269-77.
	Amgen. *A multicenter, randomized, placebo-controlled, double-blind, 12-month study to assess the effects of an oral calcimimetic agent (AMG 073) on renal osteodystrophy in hemodialysis patients with secondary hyperparathyroidism (Clinical Study Report: 20010141)* . Thousand Oaks, CA: Amgen, 2003. 2142p.
Note: Trials use different efficacy assessment phases. Study 20010141 included assessment of proportion of patients with >30% reduction in iPTH as mean over 25-52 weeks maintenance phase.	

References:

National Institute for Health and Care Excellence. Single Technology Appraisal: Etelcalcetide for treating secondary hyperparathyroidism - Final scope for invitation (Appendix B). 2016.

National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 [Internet]. London: NICE, 2013.

Health-related quality of life results in trial 20120360

A11. <u>Priority question:</u> Table 11 (company submission, page 47) states health-related quality of life (HRQoL) was measured in study 20120360 using the KDQOL-36 (Kidney Disease Quality of Life questionnaire), but results for this outcome have not been provided in the main submission. The ERG located these results in the Clinical Study Report, but no interpretation of the meaning of the results is provided. Please provide some discussion of what the results mean and guidance on how to interpret the [redacted]. For example, is a higher or lower score indicative of better quality of life? Is the [redacted] a composite of

the mean scores on each of the four subscales of this measure? Please also provide a citation for the KDQOL-36, and details of its validation.

The KDQOL-36, is a validated 36-item HRQoL survey for patients with CKD. It was developed by the RAND Corporation in 2002 as a shorter version of its original KDQOL survey. The KDQOL-36 is composed of five (sub)scales, consisting of generic quality of life assessment and kidney disease specific measures:

- *The SF-12 measure of physical (PCS) and mental (MCS) functioning (1-12*), with items about general health, activity limits, ability to accomplish desired tasks, depression and anxiety, energy level, and social activities.
- *Burden of Kidney Disease subscale (13-16*), with items about how much kidney disease interferes with daily life, takes up time, causes frustration, or makes the respondent feel like a burden.
- *Symptoms and Problems subscale (17-28b),* with items about how bothered a respondent feels by sore muscles, chest pain, cramps, itchy or dry skin, shortness of breath, faintness/dizziness, lack of appetite, feeling washed out or drained, numbness in the hands or feet, nausea, or problems with dialysis access.
- *Effects of Kidney Disease on Daily Life subscale (29-36),* with items about how bothered the respondent feels by fluid limits, diet restrictions, ability to work around the house or travel, feeling dependent on doctors and other medical staff, stress or worries, sex life, and personal appearance.

Scores are reported separately for each of the five KDQOL-36 scales. Scores for each item are transformed on to a scale of 0 to 100, with higher scores representing higher quality of life. Items in the same scale are averaged together to create the summary scale score. For reference, see: https://www.kdqol-complete.org/about/kdqol and http://www.rand.org/health/surveys_tools/kdqol.html (accessed 25/11/2016).

Study 20120360 used the KDQOL-36 instrument to assess HRQoL in enrolled haemodialysis patients. Assessments were made at baseline, week 4, week 8 and week 26. Mean results for each (sub)scale from the full analysis set are summarised in **Error! Reference source not found.**.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Baseline scores for the mental component score and the physical component score of the SF-12 were broadly comparable with those obtained from a large international sample of over 13,000 ESRD patients published this year (Perl et al., 2016). Median scores were similar to the mean scores presented above. Statistical analyses were not performed on any of these results; however, based on the descriptive numerical values obtained from each of the subscales of the KDQOL-36 instrument, it would appear that [redacted]

It should be noted that study 20120360 was of 26 weeks duration, which is sufficient to determine the superiority of etelcalcetide over cinacalcet for control of PTH levels, but is too short to capture improvements in clinical outcomes associated with this superior PTH control. The additional clinical benefit of etelcalcetide over cinacalcet would therefore not be captured in the KDQOL-36 results. In addition, study 20120360 had a double-dummy design, and so any impact of a lower pill burden and greater patient convenience of etelcalcetide versus cinacalcet (arising from its healthcare professional administration three times a week at the end of routine haemodialysis sessions, rather than daily oral therapy) is not reflected in the RCT and so would also not be captured in the results of KDQOL-36.

References:

Amgen. Clinical Study Report 20120360; 2015.

KDQOL Complete™. About the KDQOL-36™. Available at: https://www.kdqol-complete.org/about/kdqol (Accessed 25/11/2016)

Perl J, Karaboyas A, Morgenstern H, et al. Association between Changes in Quality of Life and Mortality in Hemodialysis Patients: Results from the DOPPS. Nephrol Dial Transplant. 2016. Jun 7. pii: gfw233. [Epub ahead of print].

RAND Corporation. Kidney Disease Quality of Life Instrument (KDQOL). Available at: http://www.rand.org/health/surveys_tools/kdqol.html (accessed 25/22/2016).

B: Clarification on cost-effectiveness data

Adjustments for non-adherence

B1. It is stated on page 96 of the company submission that the lag-censored analysis was pre-specified to adjust for non-adherence in EVOLVE. However, the paper by Kubo and colleagues (reference 38 in the submission) suggests that four methods of accounting for non-adherence were all planned as sensitivity analysis: lag censoring; inverse probability of censoring weights (IPCW); rank preserving structural failure time model (RPSFTM) and iterative parameter estimation (IPE). Please clarify whether any of these methods was preferred a priori. If so, please explain why.

In the presence of non-adherence it is desirable to adjust the estimates of the treatment benefit, rather than to rely solely on an unadjusted ITT analysis. Otherwise, estimates of the treatment effect will be inaccurate, and inappropriate conclusions on the effectiveness of the intervention could be drawn. The EVOLVE Clinical Trial Investigators anticipated non-adherence during the study period based on previous experience of phase 3 trials and accounted for this in the study design and planned sensitivity analyses.

In the EVOLVE statistical analysis plan (SAP), the lag-censored approach was the only pre-specified sensitivity analysis to adjust for non-adherence and was thus the preferred approach for the base case economic evaluation. The lag-censored approach was employed to account for the persistent effect of cinacalcet post-discontinuation (informed from observations in previous RCTs) and the 6-month lag period was selected *a priori* based on the clinician's judgement from the EVOLVE Executive Committee.

The EVOLVE SAP also refers to sensitivity analyses to account for commercial cinacalcet use during the study period. Specifically, a simple censored analysis was employed whereby subjects are censored at the time of initial commercial cinacalcet use. However, it is stated that *'other methods to estimate a more refined treatment effect may be performed'* and it is these methods that Kubo *et al.* explore in their analysis plan to account for non-adherence in both treatment groups. As requested in question B2, additional methodologies are discussed in our response.

References:

Kubo Y, Sterling LR, Parfrey PS, Gill K, Mahaffey KW, Gioni I, et al. Assessing the treatment effect in a randomized controlled trial with extensive non-adherence: the EVOLVE trial. Pharmaceutical statistics. 2015;14(4):368.

EVOLVE Statistical Analysis Plan. Amgen Data on File. 2012

B2. **<u>Priority question:</u> It is noted on page 97 of the company submission that some challenges were experienced in applying methods suggested in NICE Decision Support Unit technical support document 16 to adjust for non-adherence in EVOLVE outcomes needed for the economic model. In particular, it is noted that the IPCW method could not be applied to fracture and parathyroidectomy (PTx) endpoints due to the small number of events. This suggests that this method was applied to the other endpoints of interest: all-cause mortality and non-fatal CV events. It is also noted that the RPSFTM and IPE methods do not have the same data requirements. Please provide results (hazard ratios with confidence intervals) for IPCW, RPSFTM and IPE methods applied to all individual event types (all-cause mortality, fracture, non-fatal cardiovascular events and PTx) that could be evaluated. Please also provide further justification as to why the RPSFTM and IPE methods were considered not to be the most appropriate.**

The economic evaluation of etelcalcetide was informed by previous decision-analytic models that assessed the cost-effectiveness of calcimimetics. In particular: the NICE PenTAG model published by Garside et al, the OPTIMA based model of Eandi et al. and the EVOLVE-based model of Belozeroff et al. (2015). Estimates of the relative effectiveness were based on the lag-censored HRs published in the Belozeroff et al. (2015) study identified in the systematic literature review of economic evaluations. The lag-censored methodology was applied in the base case as it was the pre-specified method to account for non-adherence in the EVOLVE SAP and was based on a clinical rational of sustained treatment effect post-discontinuation. A sensitivity analysis of the lag time used has been explore in Question B3 of our response.

In order to address this question, we have provided further details on the IPCW analysis described in our original submission, and additional analyses based on the RPSFTM and IPE methodologies for each individual endpoint. An overview of each approach and the results of these are presented below.

<u>Overview of non-adherence adjustment approaches</u>

<u>Lag censoring</u>

The pre-specified lag-censoring approach essentially consists of a Cox proportional hazards regression – as such, it does not make any distributional assumptions, and one of its advantages is its simplicity.

<u>Inverse Probability of Censoring Weights (IPCW)</u>

The IPCW method aims to model the causal effect of treatment on outcomes, while accounting for time-invariant variables and time-varying confounders. In this context, time-varying confounders are variables that are affected by prior exposure to treatment and predict subsequent exposure to study drug and the outcome. The IPCW method intends to estimate the effect attributable to treatment under the assumption of no unmeasured confounders of the outcome that independently predict non-adherence.

A key principle of the IPCW method is to recreate the population that would have been observed had patients remained on assigned study drug. It does so by censoring data at the time of study drug discontinuation for non-adherent patients and assigning weights that are

proportional to the inverse of the probability of remaining on study drug given each individual patient's characteristics. The underlying assumption for IPCW is that censoring of events due to discontinuation of study drug is independent of failure time (i.e. missing at random).

However, this approach has strong limitations. One issue, for example, is model convergence, which may fail due to sample size, choice of variables, number of variables included, and due to the specification of time intervals. As a consequence of this, the inclusion of variables that are known confounders may result in model failure and can yield biased efficacy estimates if subsequently excluded.

In order to evaluate treatment effect estimates based on the IPCW analyses, covariate selection and time intervals were aligned with the methodology presented by Kubo *et al* (2015). In our original submission, we erroneously reported that results of the IPCW analysis were unavailable for the non-fatal fracture endpoint due to a small number of events in the trial – this has been corrected and the results are presented in the below.

Rank Preserving Structural Failure Time Model (RPSFTM)

The RPSFTM method is based on an accelerated failure time (AFT) model, which assumes that exposure to treatment has a multiplicative effect on a patient's observed survival time. This approach aims to estimate the efficacy of the study drug as if patients maintained their randomised treatment for the entire study duration. In the analysis, full-recensoring was applied to both arms (following Greenland 2008 Appendix G-Testing) to avoid informative censoring. The RPSFTM analysis was adjusted for the randomisation stratification factors (Diabetes status and region), as well as age, which was necessary due to the age-imbalance observed between trial arms in EVOLVE.

Iterative Parameter Estimation (IPE)

Similar to RPSFTM, IPE relates the observed failure time to an observed survival time. IPE aims to estimate the efficacy of the study drug as if patients maintained their randomised treatment for the entire study duration. However, unlike RPSFTM, the observed survival time is defined as the failure time that would have been observed had patients remained adherent to the assigned treatment.

The approach used is based on a previously published full-recensoring methodology (White Letter to Editor 2006) and is applied to the cinacalcet treatment arm. Treatment 'drop–in' for patients in the placebo arm who received commercially available cinacalcet is not accounted for in the model – as such, the analysis can be considered to provide a conservative estimate of the relative treatment effect for cinacalcet vs. placebo. As with the RPSFTM analysis, the analyses were adjusted for the randomisation stratification factors (diabetes and region) as well as for age.

Hazard ratios for the additional approaches to adjust for non-adherence

The HRs for the base case lag-censored analysis and the three additional methodologies are summarised in Table 4 below. The results are broadly consistent across all model endpoints and demonstrate consistency of the treatment effect when using the different approaches.

Table 4: Hazard ratios from the EVOLVE trial for cinacalcet vs. placebo

	Lag-censored (base case analysis)*	IPCW+	RPSFTM#	IPE#
All-cause mortality	0.80 (0.69, 0.91)	[redacted]	[redacted]	[redacted]
CV events[1] (non-fatal)	0.78 (0.67, 0.91)	[redacted]	[redacted]	[redacted]
Fractures (non-fatal)	0.73 (0.59, 0.92)	[redacted]	[redacted]	[redacted]
PTx (non-fatal)	0.25 (0.19-0.33)	[redacted]	[redacted]	[redacted]

CV, cardiovascular; ITT, intention-to-treat; PTx, parathyroidectomy

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

*Extracted from Belozeroff et al. (2015); results are adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

+Time intervals and covariates were taken from Kubo et al. (2015). Therefore, the results are adjusted for age (>65 vs. <65 yrs), sex, race, region, diabetes status, baseline iPTH, Phosphorous and Calcium including interaction terms.

Covariate adjustment consisting of the randomisation stratification factors (diabetes status and region), and age (> 65 vs. < 65 yrs)

Conclusion

The lag censored analysis was presented in the original submission as this was considered to be the most appropriate to account for non-adherence in EVOLVE. Specifically, this approach was the pre-specified sensitivity analysis in the EVOLVE SAP and was informed by previous RCTs and clinical expert judgement. Although the alternative approaches provide useful sensitivity analyses around the base case estimate, each approach has limitations that should be considered when interpreting the results.

The IPCW method is complex and relies on the “non-measured confounders” assumption (eg. data must be available on all important prognostic factors for endpoints of interest that independently predict the probability of switching). Model convergence is a challenging issue since it may fail due to sample size, choice of variables, number of variables included, or the specification of time intervals. This potentially leads to a subjective selection of covariates and biased estimates.

Both RPSTFM and IPE methods make strong assumptions on the survival time by using parametric accelerated failure time models. These methods aim to estimate the efficacy of the study drug as if patients maintained their randomised treatment for the entire study duration. However this may be an unlikely scenario in a patient population with chronic illness (such as CKD with sHPT on dialysis) given the high pill burden and other therapies required to treat co-morbid conditions. In addition, both methods rely on the assumption that the treatment effect is the same regardless of when treatment is take (ie. “common treatment effect”). This is likely implausible, because as disease progresses, it is unlikely that patients who switch to the experimental treatment in the middle of the trial will have the same treatment effect as patients originally randomised to the experimental group.

Although no methodologies are without limitations, the pre-specified lag-censored analysis provides a relatively simple and transparent methodology to assess the impact of non-adherence on the treatment effect of calcimimetic in the EVOLVE trial for the purpose of economic modelling. Sensitivity analyses using IPCW, RPSFTM and IPE are methodologically challenging and/or with strong assumptions and should be interpreted with

caution, but indicate treatment effects that are broadly consistent with those estimated with the lag censored approach. Therefore, the lag censored analysis is supported as the most robust, pragmatic and appropriate method to use.

References

White I. Estimating treatment effects in randomized trials with treatment switching [Letter to the Editor]. Statistics in Medicine 2006;25:1619–22.

Greenland S, Lanes S, Jara M. Estimating effects from randomized trials with discontinuations: the need for intent-to-treat design and G-estimation. Clinical Trials 2008; 5:5–13.

Kubo Y, Sterling LR, Parfrey PS, Gill K, Mahaffey KW, Gioni I, et al. Assessing the treatment effect in a randomized controlled trial with extensive non-adherence: the EVOLVE trial. Pharmaceutical statistics. 2015;14(4):368.

Belozeroff V, Chertow GM, Graham CN, Dehmel B, Parfrey PS, Briggs AH. Economic Evaluation of Cinacalcet in the United States: The EVOLVE Trial. Value Health. 2015;18:1079-87.

B3. <u>Priority question:</u> Sensitivity analysis of the duration of lag assumed in the lag-censored analysis for EVOLVE is presented for the primary composite outcome in EVOLVE (Table S7, p45 Chertow et al NEJM 2012, supplementary appendix). Please present this same analysis for the individual model endpoints (all-cause survival, non-fatal cardiovascular events, fractures and PTx).

In the base case analysis, a lag time of 6-months was specified *a priori* as, in the view of clinical experts, it represented the anticipated duration that the effect of altered mineral metabolism had on extra skeletal calcification. The supplementary appendix in Chertow *et al*. presents a sensitivity analysis of the assumed lag time in the lag-censored analysis for the primary composite endpoint in EVOLVE. However, in contrast to the inputs of the decision-analytic model, this analysis does not adjust for potential confounders, which is preferable due to the imbalance in baseline characteristics observed in the trial. We have therefore modified our base case estimates by applying different lag-times, and present a sensitivity analysis on

HR estimates for the four endpoints of interest using lag times of 0 months, 3 months, 9 months, 12 months and 18 months.

The HRs for cinacalcet vs. placebo based on the covariate-adjusted ITT analysis at various lag times are presented in Table 5 below. The HRs used in the base case analysis have been included for comparison.

Table 5: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo – lag time sensitivity analysis

	Lag-censored HRs[2] Base Case (6 Months)	Lag-censored HRs[2] 0 Months	Lag-censored HRs[2] 3 Months	Lag-censored HRs[2] 9 Months	Lag-censored HRs[2] 12 Months	Lag-censored HRs[2] 18 Months
Cinacalcet vs. placebo						
All-cause mortality	0.80 [0.69, 0.91]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV events[1] (non-fatal)	0.78 [0.67, 0.91]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fractures (non-fatal)	0.73 [0.59, 0.92]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTx (non-fatal)	0.25 [0.19, 0.33]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CV, cardiovascular; ITT, intention-to-treat; PTx, parathyroidectomy

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

[2]Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

[redacted].

In conclusion, the results of the sensitivity analysis demonstrate that the estimated treatment effect from the lag-censored analysis is robust to changes in the lag time evaluated. However, as the 6-month lag duration was informed by clinical expert opinion and based on the anticipated effect of altered mineral metabolism on extra skeletal calcification, we believe that the treatment effect estimate from this analysis remains the most appropriate.

References:

Kubo Y, Sterling LR, Parfrey PS, Gill K, Mahaffey KW, Gioni I, et al. Assessing the treatment effect in a randomized controlled trial with extensive non-adherence: the EVOLVE trial. Pharmaceutical statistics. 2015;14(4):368.

EVOLVE Statistical Analysis Plan. Amgen Data on File. 2012

Amgen Data on file_lag censored sensitivity analysis (lag time)

B4. <u>Priority question:</u> It is noted on page 101 of the submission that the rationale for the surrogate endpoint used for the extrapolation in the Section 5.2.6.3 is

that it was the primary outcome for the etelcalcetide trials (>30% reduction in PTH from baseline). However, it is likely that absolute control of PTH levels (e.g. achievement of mean PTH within ≤ 300 pg/ml during the efficacy assessment phase) would be a better predictor of the incidence of long-term clinical outcomes (mortality, cardiovascular events, fractures and PTx) rather than a percentage change. Please conduct a scenario analysis to test the sensitivity of the estimated hazard ratios and ICERs to extrapolation of the etelcalcetide trials to EVOLVE endpoints using an absolute measure of PTH control (achievement of PTH target range).

The rationale for using the PTH reduction of at least 30% from baseline as the surrogate endpoint for extrapolation in the base analysis was that this is the pre-specified primary outcome of the etelcalcetide trials and is regarded by clinicians to be clinically meaningful. However, we acknowledge that achievement of PTH ≤ 300 pg/mL in observational studies has been associated with a reduced risk of all-cause mortality (compared with PTH values >300 pg/mL), decreased bone turnover and improved bone histology, which would support the use of this target as an appropriate surrogate endpoint to extrapolate to the clinical endpoints measured in EVOLVE. As requested, we have provided hazard ratios and cost-effectiveness results based on this absolute measure of PTH control.

As discussed in the submission dossier, the proportion of patients with mean PTH ≤ 300 pg/mL during the EAP was significantly higher for the etelcalcetide group compared with placebo (51.5% vs 4.9%; P<0.001) in the pooled analysis of the placebo controlled trials. In the active-controlled trial, treatment with etelcalcetide also resulted in a higher proportion of patients achieving mean PTH ≤ 300 pg/mL during the EAP compared with the cinacalcet group (38.5% vs. 26.2%; P<0.001).

Two approaches were considered for extrapolation of the etelcalcetide trials to EVOLVE endpoints using the absolute measure of PTH control (≤ 300 pg/mL during the EAP). In the first approach, the same methodology used in the base case analysis was applied. However, due to differences between the eligibility criteria of the etelcalcetide trials the absolute outcome measure is more likely to be achieved for the placebo-controlled trials (baseline PTH >= 400 pg/mL) than in the head-to-head trial (baseline PTH >= 500 pg/mL). Therefore, we also explored an approach that would account for the differences in the baseline PTH. In this analysis, the share of subjects that achieved the target PTH for placebo and etelcalcetide were taken from the placebo-controlled trials only. For cinacalcet, the relative risk of achieving PTH $\leq$300pg/mL in the head-to-head trial was applied. We would like to note that in terms of extrapolation this approach is equivalent to taking the share of patients that achieved PTH $\leq$300pg/mL from the head-to-head trial and applying the relative risk based on the placebo-controlled trials. This is due to the fact that the probabilities would solely be re-scaled linearly. The HRs for both approaches are presented in Table 6.

Table 6: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo – lag time sensitivity analysis

	Extrapolation based on "PTH <= 300 pg/mL" (pooled analysis) [95% CI]	Extrapolation based on "PTH <= 300 pg/mL" (percentage of patients for cinacalcet based on RR from head-to-head trial) [95% CI]
Etelcalcetide* vs. PB/VD		

All-cause mortality	[redacted]	[redacted]
CV events[1] (non-fatal)	[redacted]	[redacted]
Fractures (non-fatal)	[redacted]	[redacted]
PTx (non-fatal)	[redacted]	[redacted]
Etelcalcetide* vs. Cinacalcet*		
All-cause mortality	[redacted]	[redacted]
CV events[1] (non-fatal)	[redacted]	[redacted]
Fractures (non-fatal)	[redacted]	[redacted]
PTx (non-fatal)	[redacted]	[redacted]

CV, cardiovascular; ITT, intention-to-treat; Ptx, parathyroidectomy; CI, confidence interval; RR, relative risk; *In addition to PB/VD

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

The incremental costs, QALYs and corresponding ICERs for both comparators are presented in the sub-sections below. Please note, the cost-effectiveness analyses presented in here are based on the anticipated list price of etelcalcetide. Amgen has proposed a patient access scheme (PAS) to the Department of Health, which is under consideration by the PAS Liaison Unit.

Broad licensed indication – etelcalcetide (plus PB/VD) vs. PB/VD

The results for both scenarios based on the extrapolation of the etelcalcetide trials to EVOLVE using the absolute measure of PTH control are presented in Table 7 for the broad licensed population. Incremental costs are largely consistent with the base case analysis and increase slightly in both cases, primarily due to the lower HRs observed for all-cause mortality. However, this is associated with a gain in the incremental QALYs which increase by 0.056 and 0.138 for the 'pooled' analysis and 'adjusted' analysis, respectively. As a result, there is a notable decrease in the calculated ICERs when extrapolating based on the absolute measure of PTH control.

It should be noted that when the same methodology as used in the base case analysis is applied to the absolute measure of PTH, the analysis will likely be biased due to the differences in baseline PTH between the placebo-controlled and active-controlled trials. This was not the case for the relative reduction in PTH used in the base case analysis, as this was consistent across the pre-specified baseline PTH subgroup analyses in both the placebo-controlled and head-to-head clinical trials (see Sections 4.8.1 and 4.8.2 of the original submission). As such, the scenario where a treatment adjustment is applied likely provides a more appropriate estimate of the cost-effectiveness.

Table 7: Etelcalcetide (plus PB/VD) versus PB/VD alone – results of sensitivity analyses

	Total Cost	Δ Cost	Total QALYs	Δ QALYs	ICER
Base Case Analysis					
Etelcalcetide*	[redacted]	[redacted]	4.109	-	[redacted]
PB/VD	[redacted]	[redacted]	3.788	0.321	[redacted]
Extrapolation based on "PTH <= 300 pg/mL" (poled analysis)					
Etelcalcetide*	[redacted]	[redacted]	4.252	-	[redacted]

PB/VD	[redacted]	[redacted]	3.788	0.463	[redacted]
Extrapolation based on "PTH <= 300 pg/mL" (percentage of patients for cinacalcet based on RR from head-to-head trial)					
Etelcalcetide*	[redacted]	[redacted]	4.166	-	[redacted]
PB/VD	[redacted]	[redacted]	3.788	0.377	[redacted]

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

Refractory SHPT – etelcalcetide (plus PB/VD) vs. cinacalcet (plus PB/VD)

Results in the refractory SHPT population vs. cinacalcet are aligned with the conclusions presented in the section above. Extrapolation from the etelcalcetide trials based on the absolute measure of PTH control results in decrease in the associated ICERs for each scenario explored. The primary driver of this change is the incremental QALY gains associated with etelcalcetide due to the improved all-cause mortality HR estimate.

Table 8: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of sensitivity analyses

	Total Cost	Δ Cost	Total QALYs	Δ QALYs	ICER
Base Case Analysis					
Etelcalcetide*	[redacted]	[redacted]	4.109	-	[redacted]
Cinacalcet*	[redacted]	[redacted]	4.040	0.069	[redacted]
Extrapolation based on "PTH <= 300 pg/dl"					
Etelcalcetide*	[redacted]	[redacted]	4.252	-	[redacted]
Cinacalcet*	[redacted]	[redacted]	4.040	0.212	[redacted]
Extrapolation based on "PTH <= 300 pg/dl" (with adjustment for trial differences)					
Etelcalcetide*	[redacted]	[redacted]	4.166	-	[redacted]
Cinacalcet*	[redacted]	[redacted]	4.040	0.126	[redacted]

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

In conclusion, the analyses based on achievement of an absolute PTH ≤300pg/mL yields ICER estimates that are lower than our base case approach, which was based on the primary endpoint of the etelcalcetide clinical trials, and indicates that our base case approach is highly conservative.

References

European Medicines Agency. CHMP Assessment Report: Parsabiv. 2016.

Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SH, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on

chronic hemodialysis: the DOPPS study. Clinical journal of the American Society of Nephrology : CJASN. 2015;10(1):98-109.

Behets G, Spasovski G, Sterling L, Goodman W, Spiegel D, De Broe M, et al. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015;87(4):846-56.

Discontinuation rates

B5. Priority question: Please provide one-year discontinuation rates for cinacalcet from the EVOLVE trial by region (USA, Europe, and other regions).

As requested, discontinuation rates at 12 months by region in the EVOLVE trial are presented in Figure 1. These are based on post hoc subgroup analyses and should be interpreted with caution, but confirm discontinuations in each region were broadly consistent with the overall discontinuation rates.

Figure 1: Discontinuation rates at 12 months - Study 20050182 (EVOLVE) (safety analysis set)

	Cinacalcet			Placebo		
	N	n	Discontinuation rate at 12 months (%)	N	n	Discontinuation rate at 12 months (%)
Overall	1938	558	29.4	1923	631	33.6
USA	712	192	27.7	709	246	35.8
Europe	593	197	33.8	587	227	39.7
Other	633	169	27.2	627	158	25.6

Safety analysis set: all randomized subjects who received at least 1 dose of Investigational Product.
Discontinuation rate at 12 months was calculated using the Kaplan-Meier method.
N: number of subjects in the safety analysis set.
n: number of subjects discontinued investigational product by 12 months.

References:

Amgen data on file. EVOLVE discontinuations by region; November 2016.

B6. Priority question: Please provide time to discontinuation data, if available, for the open-label extension studies 20120231 and 20120213.

Study 20120231 (OLE1)

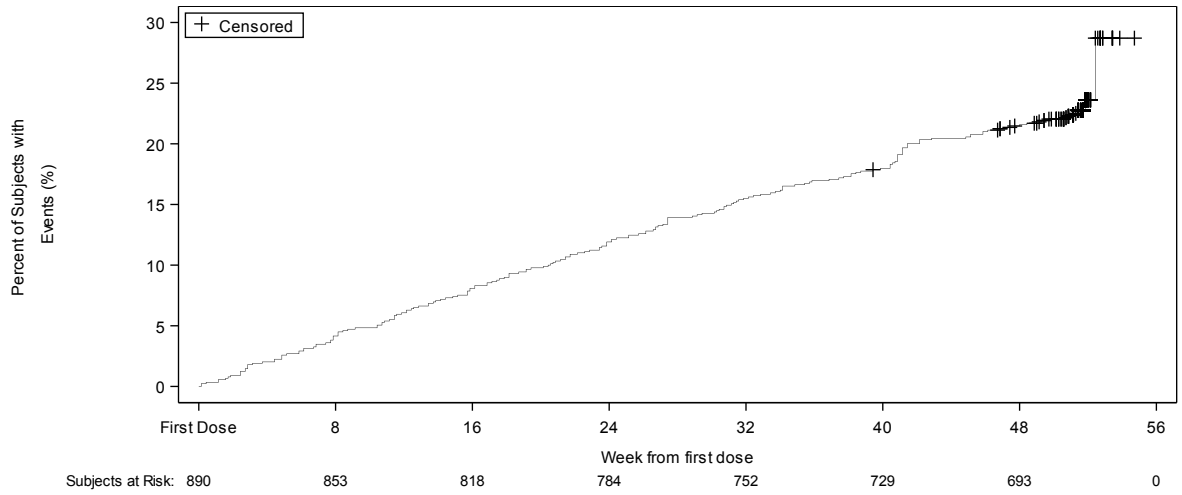
Study 20120231 was a 52-week open label extension study that enrolled a total of 891 patients from the phase 3 placebo-controlled trials (studies 2012029 and 20120230) and the single-arm switch study (20120359) who had completed treatment and follow-up or who had discontinued from treatment due to rising PTH levels. Patients initiated etelcalcetide treatment at the 30-day follow-up visit of the parent studies (i.e. after a 30 day washout period), at a starting dose of 5 mg 3 times a week regardless of treatment they had received in the parent study. They received etelcalcetide for up to 52 weeks, which included an initial 16 week dose

titration phase followed by a maintenance phase. Patients were treated to target PTH levels ≤300 pg/mL, while maintaining appropriate serum cCa levels.

Time to discontinuation data are available based on the safety analysis set, which included all patients who received at least one dose of etelcalcetide in the study (890 of the 891 enrolled patients). These data are presented in Figure 6, with time to discontinuation of etelcalcetide calculated as time from the first dose of etelcalcetide to etelcalcetide stop date for patients who discontinued etelcalcetide for any reasons excluding death and treatment completed. For patients who died or completed the treatment, data were censored to the last etelcalcetide dose date.

A total of 682 out of the 891 enrolled patients (76.5%) completed the 52-week etelcalcetide treatment period. The most common reasons for discontinuing etelcalcetide were patient request (53 patients, 5.9% of enrolled patients), protocol specified reasons (50 patients, 5.6% of enrolled patients, of which 43 patients discontinued to receive kidney transplant), and adverse events (41 patients, 4.6% of enrolled patients) (Study 20120231 CSR).

Figure 2: Time to discontinuation of etelcalcetide - Study 20120231 (Safety Analysis Set)



Time to discontinuation of IP is calculated as first dose of IP to IP stop date for subjects who discontinued IP for any reasons excluding death and completed IP.

For subjects who completed the IP or had death, censor time to discontinuation of IP to the last IP date.

Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/hta/figures/f-km-fd-amg416.sas
Output: f1-01-002-km-fd-amg416-231.rtf (Date Generated: 29NOV2016:17:17:02) Source Data: adam231.adsl

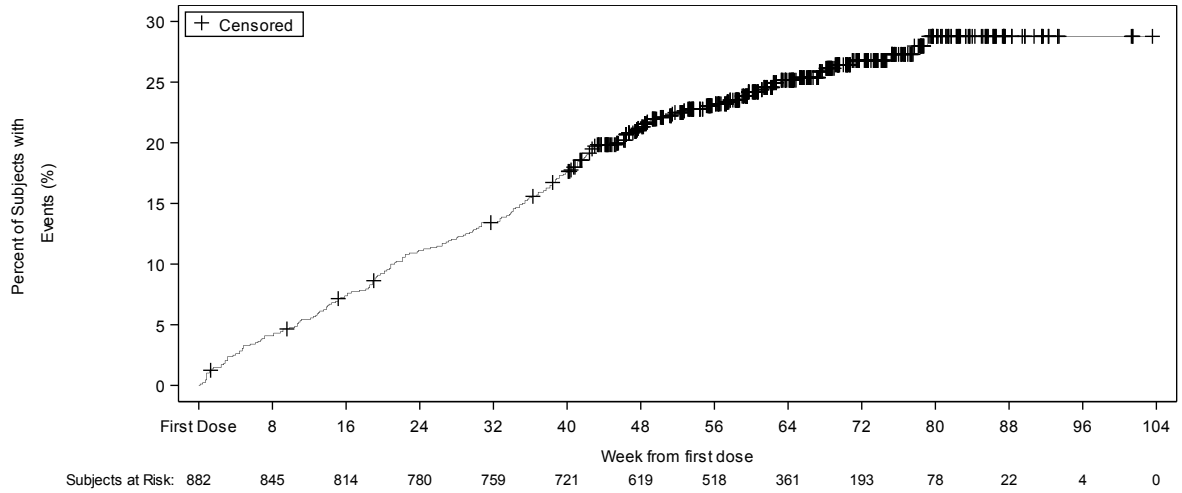
Study 20130213 (OLE2):

Study 20130213 is an ongoing open label extension study that is planned to run until around 2.5 years after the first patient was enrolled. Patients were enrolled from the 20120231 (OLE1 study) and a small single-arm study (20120344) without a washout period and continued on the etelcalcetide dose they were receiving in those studies. Additional patients were enrolled from the phase 3 active-controlled etelcalcetide study (20120360), following a 30-day washout, and initiated etelcalcetide at a dose of 5 mg (before amendment) or 2.5 mg (after amendment) 3 times per week, regardless of treatment they had received during that parent study. Patients were treated to target PTH levels between 2 and 9 times the upper limit of normal for the assay.

Time to discontinuation data are available based on a recent interim analysis (data cut off March 18 2016) in 882 patients comprising the safety analysis set (i.e. patients who had received at least one dose of etelcalcetide in this study) (Figure 3), with time to discontinuation of etelcalcetide calculated as time from the first dose of etelcalcetide to etelcalcetide stop date for patients who discontinued etelcalcetide for any reasons excluding death and treatment completed. For patients who died or completed the treatment, data were censored to the last etelcalcetide dose date.

The proportion of patients completing 52 weeks of treatment is similar to that observed in study 20120231 (OLE1), at around 75-80% based on Figure 3. Based on the interim analysis (data cut off March 18 2016), of 902 enrolled patients, 1(0.1%) patient completed etelcalcetide treatment, 220 (24.4%) patients discontinued etelcalcetide. The most common reason for discontinuing etelcalcetide were patient is to receive kidney transplant 62 (6.9%), patient request 51 (5.7%) and death 44 (4.9%). (Amgen data on file)

Figure 3: Time to discontinuation of etelcalcetide - Study 20130213 (Safety Analysis Set, data cut off March 18 2016)



Time to discontinuation of IP is calculated as first dose of IP to IP stop date for subjects who discontinued IP for any reasons excluding death and completed IP.

For subjects who completed the IP or had death, censor time to discontinuation of IP to the last IP date.

Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/hta/figures/f-km-fd-amg416.sas
Output: f1-01-003-km-fd-amg416-213.rtf (Date Generated: 29NOV2016:17:17:02) Source Data: adam213a.adsl

In our economic model, etelcalcetide discontinuation is modelled based on cinacalcet discontinuation observed in the large EVOLVE trial, as the head-to-head study (study 20120360) observed no significant difference in discontinuation rates between etelcalcetide and cinacalcet, and EVOLVE was a large study with long patient follow up (Chertow et al. 2012).

It is not appropriate to directly compare the discontinuation rates for etelcalcetide observed in the open-label extension studies above with those derived from the EVOLVE trial, as patients enrolled in the open-label extension studies represent a selected group with significant prior etelcalcetide experience and exposure. However, the following are of note:

- The 6 month discontinuation rate for etelcalcetide observed in the phase 3 etelcalcetide trials (16% in the placebo-controlled trials and 20% in the active-

controlled trial – see section 4.5.1 of our original submission) is similar to the rate at 6 months derived for cinacalcet from EVOLVE (and assumed for etelcalcetide in our model) (see Figure 17 in section 5.2.12.1 of our original submission).

- The 1 year persistence rate derived for cinacalcet from the EVOLVE trial (and assumed for etelcalcetide in our model) was 72% (based on Kaplan-Meier curve – see section 5.2.12.1 of our original submission), which is numerically lower than the 76.5% persistence at 1 year observed with etelcalcetide in the final analysis of the 52-week open-label extension study 20120231 (OLE1) (and the similar result in the interim analysis of the 20130213 (OLE 2) study).

The discontinuation data available for etelcalcetide from the phase 3 RCTs and the open-label extension studies above therefore support our modelling of etelcalcetide discontinuation as a conservative approach.

References:

Amgen data on file. Time to discontinuation of etelcalcetide - Study 20120231; November 2016

Amgen data on file. Time to discontinuation of etelcalcetide - Study 20130213; November 2016

Other

B7. <u>Priority question:</u> Please provide the absolute event rates (number of events and number of patients) for the cinacalcet and placebo arms for each of the pre-defined 'region' and 'PTH group' subgroups in the EVOLVE trial (as shown in Figure S2, p. 11 of Chertow et al. NEJM 2012 supplementary appendix) for the following outcomes: all-cause mortality, the non-fatal cardiovascular event composite (myocardial infarction, hospitalisation for unstable angina, heart failure, peripheral vascular event), stroke, non-fatal fractures and PTx.

In line with the request of the ERG, the absolute event rates for cinacalcet and placebo for all-cause mortality, the non-fatal cardiovascular event composite (myocardial infarction, hospitalisation for unstable angina, heart failure, peripheral vascular event), stroke, non-fatal fractures and PTx, by the pre-defined 'region' and 'PTH group' subgroups in the EVOLVE trial are presented in the Tables below. However, there are significant limitations to these requested analyses, which must be noted before considering these results:

1) As reported in our original submission, the EVOLVE trial results were confounded by a chance imbalance in age between the cinacalcet and placebo arms, a higher incidence of treatment discontinuation than was expected in both arms, and use of commercially available cinacalcet in a high proportion of placebo recipients before the occurrence of a primary event. These confounding effects biased the primary unadjusted ITT analyses against cinacalcet in the EVOLVE trial. For this reason, our economic model uses event rates based on co-variate adjusted, lag-censored analyses of the EVOLVE trial, which appropriately adjust for these specific confounding issues. In contrast, the results presented in Figure S2, p. 11 of Chertow et al. NEJM

2012, supplementary appendix, and the figures requested by the ERG and presented in the tables below, are not adjusted for these confounding factors.

2) The primary endpoint of the EVOLVE trial was a composite of time until death and major CV events (myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event). Stroke, non-fatal fractures and PTx were secondary endpoints (Chertow et al., 2012). While the EVOLVE trial pre-defined these 'regions' and 'PTH thresholds' in the analysis of the primary composite endpoint, the ERG request requires analyses by 'regions' and 'PTH thresholds' for individual components of this, and for secondary endpoints. The analyses requested by the ERG therefore represent post hoc analyses in much smaller subgroups than included in our submission.

The figures presented in the tables below are therefore provided to meet the request of the ERG, but are subject to significant limitations, which warrant caution in their interpretation and use. Post hoc analyses of small subgroups are prone to chance imbalances in known and unknown risk factors for specific events, and can lead to spurious results.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

References:

Amgen data on file. EVOLVE absolute event rates by region_PTH: Mortality; November 2016

Amgen data on file. EVOLVE absolute event rates by region_PTH: CV events; November 2016

Amgen data on file. EVOLVE absolute event rates by region_PTH: Stroke; November 2016

Amgen data on file. EVOLVE absolute event rates by region_PTH: Non-fatal Fracture; November 2016

Amgen data on file. EVOLVE absolute event rates by region_PTH: PTx; November 2016

B8. Please clarify whether intravenous administration of etelcalcetide would incur additional costs to the NHS: more nurse time and/or increased duration of the haemodialysis session.

Based on feedback from UK nephrologists and an investigator in the etelcalcetide clinical trial programme, etelcalcetide is unlikely to incur additional cost or resource based on the route of administration.

As per the SPC: 'Etelcalcetide is administered into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back or intravenously after rinse-back.'

Administering the bolus injection would have a very small impact on nurse time and would not increase the overall length of the dialysis session. As such, the administration of etelcalcetide would fall within the remit of a typical dialysis session and would be unlikely to incur additional costs.

C: Textual clarifications and additional points

C1. Please provide the full clinical study report for study 20120231 (reference 32 in the submission; only a synopsis was provided with the original submission) and Amgen data on file for study 20120213 (reference 33, 'interim analysis summary').

These references are provided with this response.

C2. <u>Priority question:</u> The EVOLVE trial is a key data source for estimated clinical effects in the de novo economic evaluation in chapter 5 of the company submission. Please provide a copy of the Clinical Study Report for this trial.

This reference is provided with this response.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: British KIdney Patient Association

Your position in the organisation: Policy Director

Brief description of the organisation: The British Kidney Patient Association (BKPA) is the leading national charity which works to improve quality of life for kidney patients through advocacy, direct grants, educating and informing patients, counselling and funding patient-centred research.

We are funded through the investments our founder (the mother of a kidney patient herself) made through her work, and through our present fundraising activities. We don't have members but through our work are directly in contact with 100s of patients every month, especially through our advocacy officers, counselling and grant giving.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Patients state that their main symptoms are bone pain, stomach pain & depression; a patient of 45 stated that it made her walk as though she was in her 80s. Aching bones cause sleeplessness and reduce mobility. The mental challenges of this complication of kidney failure can exacerbate depression.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients want to be able to walk around, to be able to sleep, to feel less nauseous. Some of this could be addressed by reduction in pain.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The BKPA is aware of the various treatments for early control of hyperphosphataemia through diet, alfacalcidol, sevalamer etc but that they represent a challenging regime (e.g some have be taken with every meal) and that the further complications of hyperparathyroidism can set in anyway. The further treatments of which the BKPA is aware are the cinalcalcet drug or surgery. In 2005, before this drug became available, removal of the parathyroid gland was the only option, although for some patients the PTH levels can normalise following transplant. However cinacalcet itself has side effects, such as nausea, and parathyroidectomy is major surgery which carries risks, especially to patients who are already vulnerable to vascular and infection complexities. Surgery to remove the parathyroid gland is not always successful as sometimes it cannot be located.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)

- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Patients and carers have indicated that the following will be advantages:

Reduction of pain

Increase in mobility

Reduction in need for surgical intervention

Flexibility in receiving treatment (i.e. on dialysis) but note that some people dialyse at home and would want to be able to self-administer as they do with current drugs.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

The key interest shown by kidney patients is in the opportunity to have a more effective treatment than those which are presently available and which would relieve the serious and very unpleasant impact of secondary hyperparathyroidism.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The main issue is that current NHS treatments do not work for some kidney patients.

Please list any concerns patients or carers have about the treatment being appraised.

Please note the earlier comment about how the drug would be administered for people who are on home dialysis and are less likely to want to come into hospital 3 times a week to receive this treatment, and people with transplants for whom the same comment would apply.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes No

If you answered 'no', please skip the rest of section 7 and move on to

section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Please note that there are kidney patients who are or may be given current treatments off-label as they are not on dialysis. They may be post-transplant or pre-dialysis and still have secondary PTH and be symptomatic. We would not wish new guidance to impact on this flexibility. There may also patients with a PTH under 800 who benefit from treatment. New treatments should continue these patients also.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

Yes No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Secondary hyperparathyroidism affects both mental and physical health
- Secondary hyperparathyroidism is a source of pain and affects mobility and sleep
- The patients who commented on this possible new treatment were not aware of it but welcome innovation

- Secondary hyperparathyroidism is difficult to treat and drug regimes are burdensome with surgery carrying extra risk and not always successful

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Kidney Research UK
Your position in the organisation: Research Communications Officer
Brief description of the organisation: Kidney Research UK is the leading charity dedicated to research into kidney disease in the UK. We rely almost wholly on the generous donations of the UK public and we believe that everybody deserves a life free of kidney disease.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Symptoms are similar in both primary and secondary hyperparathyroidism. They include fatigue, depression, confusion, loss of concentration, drowsiness, nausea, loss of appetite, stomach pain. If untreated, it can cause hypertension and other coronary-like symptoms.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Kidney Research UK undertook an online patient survey on the topic of treatment options for secondary hyperparathyroidism. The survey was sent to 1,949 renal patients and contained 13 questions in total. We received a 9.5% response rate (185 responses):
http://www.kidneyresearchuk.org/file/parathyroidism_survey_results_112016.pdf

Patients in our survey commented that they wanted the condition to be well controlled. Of the respondents with secondary hyperparathyroidism 43.36% (49 patients) preferred controlling symptoms with diet, 33.63% (38 patients) preferred phosphate binders, 27.43% calcimimetics (31 patients), and only 26.5% (30 patients) preferred surgery (NICE's current recommendation is surgery as the first-line treatment).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these

treatments and which are preferred and why?

Most patients with secondary hyperparathyroidism are treated with a combination of dietary restriction of phosphate intake, calcium- and non-calcium-based phosphate binders, and vitamin D analogues. Many patients find taking phosphate binders inconvenient, as these are large tablets, difficult to chew or swallow that have to be taken with each phosphate-containing meal. However, reduction of phosphate absorption would remain a clinical need even if additional treatments were available for hyperparathyroidism, because phosphate retention has adverse consequences over and above stimulation of hyperparathyroidism.

Patients with severe hyperparathyroidism despite these measures are offered partial or total surgical parathyroidectomy, or, if unfit for surgery, a calcimimetic. Calcimimetics are well-tolerated but can cause nausea.

Surgical parathyroidectomy is currently considered the 'gold standard' treatment for severe hyperparathyroidism, but has several drawbacks, including:

- The need for surgery under general anaesthesia
- The cosmetic effects of a scar across the neck
- The psychological effects for the patient
- The need for intensive post-operative monitoring of serum calcium, due to the risk of hypocalcaemia caused by 'hungry bone' syndrome; frequent blood tests and adjustments of the dosage of calcium supplements and activated vitamin D analogues are necessary, often for several months after surgery
- The need for life-long calcium and activated vitamin D supplementation
- The risk of low bone turnover bone disease caused by over-correction of hyperparathyroidism: low bone turnover is associated with an increased risk of fractures and of vascular calcification

In our patient survey, we asked patients whether they were happy with their treatment and there was an even split in responses: 22 patients who received surgical treatment were happy, 24 patients who were treated through diet control were happy, 24 patients who were treated with calcimimetics were happy, and 22 patients who were treated with phosphate binders were happy. This clearly shows that different treatment options work for different people.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:
• the course and/or outcome of the condition

- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Patients expect to gain relief from symptoms and better control. We have found from our survey that patients are knowledgeable in relation to the options available. They expect to be able to make an independent and informed decision as to which treatment option is appropriate for them.

Patients dialysing in hospital will not have to worry about administering another oral medication, as this will be administered through IV (the first time a calcimimetic is available in this formulation), thereby minimising the pill burden.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Avoiding the trauma of surgery came high in our responses. Additional comments from patients in our survey included:

- Hopefully this [calcimimetics] would be less invasive and pleasant to take. They were not available many years ago when I had my operation.
- Least invasive option is always better
- Definitely avoid surgery where possible. Diet the best but hard when restricted so much so understand tablets probably better.
- I would have preferred a method other than surgery, but none was available 10 years ago

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

As per our response to 3, of the respondents with secondary hyperparathyroidism 43.36% (49 patients) preferred controlling symptoms with diet, 33.63% (38 patients) preferred phosphate binders, 27.43% calcimimmetics (31 patients), and only 26.5%

(30 patients) preferred surgery (NICE's current recommendation is surgery as the first-line treatment).

From our survey we've found that different patients want different treatment options. Patients would like their clinician to be able to discuss a greater range of treatment options than is currently available through NICE guidance.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Patients in our survey have commented:

- Surgery would be my absolute last resort as I have enough with 2 kidney transplants, plus related complications, and fistula operation.
- Definitely avoid surgery where possible. Diet the best but hard when restricted so much so understand tablets probably better.
- Obviously I would have preferred a method other than surgery, but none was available 10 years ago
- The Parathyroidectomy was traumatic and I lost my voice post op for about 6 weeks.
- I was not really given an option as to whether I had the operation or not. I was told that it was more cost effective than being on long term medication.

- It's very hard to make an informed decision on this as, although I`ve had the operation, I am still on Phosphate binders and [calcimimetics] with the usual restricted diet - it makes me wonder if the surgery was worth it.

- Have been told I may need surgery, not keen, so if there is a simpler answer, it will be good. Otherwise I would take this latest drug if necessary, hopefully without too many side effects

Please list any concerns patients or carers have about the treatment being appraised.

Some patients have reported nausea and vomiting.

One patient commented: 'I am taking too much medication to attribute side effects that I am getting, to [calcimimetics].'

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

As per our response to 3, of the respondents with secondary hyperparathyroidism 43.36% (49 patients) preferred controlling symptoms with diet, 33.63% (38 patients) preferred phosphate binders, 27.43% calcimimmetics (31 patients), and only 26.5% (30 patients) preferred surgery (NICE's current recommendation is surgery as the first-line treatment).

From our survey we've found that different patients want different treatment options. Patients would like their clinician to be able to discuss a greater range of treatment options than is currently available through NICE guidance.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who would otherwise be offered surgical parathyroidectomy could benefit from a well-tolerated IV drug treatment that could allow controlled reduction of parathyroid activity, avoiding the disadvantages of surgical parathyroidectomy.

Patients who have difficulty in swallowing phosphate binder tablets, or remembering to take tablets regularly might benefit; such patients would benefit more from an injectable calcimimetic.

Patients who do not want or are not suitable for surgical parathyroidectomy would also benefit.

Patients who struggle with their tablet burden would also benefit as it can be administered through IV at the end of a dialysis session.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware of.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

y Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Please see our survey results.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

None that we're aware of.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

y Yes ☐ No

If yes, please provide references to the relevant studies.

8. http://www.kidneyresearchuk.org/file/parathyroidism_survey_results_112016.pdfEquality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality,

ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

In 2009 NICE produced a Clinical Guideline Medicines Adherence: involving patients in decisions about prescribed medications and supporting adherence (CG76).

This guideline enables patients to make informed decisions about their prescribed medication. Patients therefore should be given a choice if they want a surgical or non-surgical treatment.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

There are groups of patients who struggle with currently available oral treatments, due to too high a pill burden, or difficulty in swallowing. There are also groups of patients for whom surgery is contraindicated or not a desired option.

Reducing the pill burden in dialysis patients helps increase medicines adherence and should lead to an improvement in treatment outcomes ref *Medication Burden in CKD* Parker et al www.britishrenal.org

Furthermore daily pill burden in dialysis patients is one of the highest reported in any chronic disease state. Higher pill burden is associated with poor health related quality of life (HR_QOL), ref *Pill Burden ,adherence, hyperphosthemia, and quality of life* Chui et al Clin J Am Nephrology 2009, June 1089-96. As the first IV calcimimetic available, etalcalcetide IV will offer distinct patient advantages.

9. Other issues

Do you consider the treatment to be innovative?

y Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This can be administered at the end of a dialysis session and therefore does not add to the pill burden and avoids the psychological trauma of surgery.

Are there any other issues that you would like the Appraisal Committee to consider?

No.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- 75% of patients in our survey do not want surgery, which is currently the 'gold standard' NICE recommended option.
- Different treatment options suit different patients, particularly with regard to this condition as shown by our survey.
- As this treatment can be given via IV at the end of a dialysis session this means it does not inconvenience the patient or the healthcare professional.
- Calcimimetics are well-tolerated.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Etelcalcetide for treating secondary hyperparathyroidism

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Organisation: Queen Elizabeth Hospital, University Hospitals of Birmingham

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? *Yes*
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
  No, I have not been involved in the trials
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
  I am renal consultant at UHB NHS Trust. We treat many patients with this condition.
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
I have no links in any form to the tobacco industry.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Secondary hyperparathyroidism is a common complication for patients with renal disease leading to increased circulating levels of parathyroid hormone (PTH). Secondary hyperparathyroidism complications include renal osteodystrophy and the accompanying abnormalities in bone metabolism. These abnormalities are associated with fractures, poor quality of life, cardiac dysfunction and increased mortality.

Despite the advances in understanding of the pathways involved, the management of secondary hyperparathyroidism is still complex and difficult to achieve. The KDIGO guidelines 2009 recommend maintaining the serum PTH levels between 2x-9x the upper limit of the normal range, adjusting treatment based on the change over time of the serum PTH level rather than a single result. The wide range for the PTH target comes from the lack of good evidence and the variation in results seen in observational studies. The guidance for the PTH target was based on 2C evidence and observational data. Some studies showed a U shaped curve with mortality, others a linear relationship, and the PTH level at which point the mortality increased varied from 400-600 pg/ml. The recommended range was based on 'extremes of risk' and aims to take into account the significant variability in PTH assays. There are no RCTs in this area.

Since the guidelines were produced two large observational studies have shown about a 15% increase in mortality when the PTH is greater than 600 pg/ml.

The new KDIGO guidelines have been for public review and should be published later this year and therefore may change. The new guidance has not changed the suggested PTH 'target' but has slightly changed the wording of how they would recommend treatment. A proposed change in the new guidance states 'In patients with CKD Stage 5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics and calcitriol, or vitamin D analogs. (2B)'. This statement suggests we should not prioritise one treatment over the other for management of the patients and each one could be a used first-line if felt appropriate. Despite this I would not expect any of my colleagues to consider this medication, or Cinacalcet HCl, unless other 'standard' treatments had been attempted.

To achieve the PTH target, management of the phosphate and calcium levels is required and this occurs alongside the administration of, mostly oral, vitamin D. If these treatments fail then the parathyroid glands become over-stimulated and develop adenomatous change resulting in 'tertiary' hyperparathyroidism. When this develops the glands have limited response to the normal negative feedback mechanisms and there is down regulation of the calcium sensing receptor (CaSR) and vitamin D receptor leading to even more difficulty in the patient management. The likelihood of developing tertiary hyperparathyroidism increases with time on dialysis and patients then progress to either requiring treatment with Cinacalcet HCl, if appropriate or undergo parathyroidectomy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Surgical parathyroidectomy is the main treatment option and previous studies have shown that after 10 years of dialysis about 10-15% of the dialysis population will have undergone this procedure and about 20% after 20 years. Unfortunately hyperparathyroidism recurs in about 6-13% of patients 2 years post surgery. This is thought to be secondary to regrowth of incompletely excised glands. Further surgery is much more hazardous. Mortality from parathyroidectomy is stated at about 1-2% but some complications are well recognised such as severe hypocalcaemia, hyperkalaemia and damage to the recurrent laryngeal nerve (10%) which is usually, but not always, temporary.

Cinacalcet HCl is the main alternative but currently is only funded if the PTH is greater than 800pg/ml and the patient is unsuitable to proceed with a parathyroidectomy. Cinacalcet HCl is an oral calcicimetic agent that acts as an allosteric modulator of the calcium sensing receptor (CaSR) on the surface of the parathyroid cells. Cinacalcet HCl increases the receptor sensitivity to extracellular calcium and reduces PTH concentrations and has been shown to improve the number of patients achieving bone metabolism targets. The CaSR is down-regulated when the Parathyroid gland undergoes adenomatous changed therefore limits the effectiveness of calcimimetic. There is up regulation of the CaSR after exposure to calcimimetics, however the parathyroid gland is more responsive at the lower levels of PTH.

Cinacalcet HCl lowers serum PTH, calcium and FGF23 levels and this has been shown in many studies. Lowering calcium is thought to be an advantage as many of the phosphate binders and vitamin D treatments lead to an increase in serum calcium levels. The lower calcium allows other medications to be increased and therefore increase the overall treatment tolerated. Studies have shown that increased FGF23 levels are associated with mortality in patients with renal disease and therefore lowering these is thought to be beneficial.

The long term benefits have been studied with Cinacalcet HCl with the EVOLVE study. The primary endpoint was non-significant though two thirds of the study population dropped out of the study and there was significant cross-over. Despite randomisation there was also a significant age difference between arms and when this is taken into account an improvement in mortality was shown in post-hoc analysis. Further analysis of the EVOLVE study has shown that in patients whom had a fall in their FGF23, a decrease in mortality was shown.

The use of Cinacalcet HCl does have some geographical variation due to variations in practice though I do not think this is significant. The side effect profile of Cinacalcet HCl also limits its use in some patients as some patients cannot tolerate higher doses. I have been involved in a patient education project and this showed patients' were not as adherent to their medication as we would like and needed more education to understand why adherence was beneficial.

There is a proportion of patients for which Cinacalcet HCl does not work and the treatment is no longer continued if the patient does not have a 30% drop in the PTH after 3-6 months.

Etelcalcetide is an intravenous calcimimetic with different pharmacokinetics to Cinacalcet HCl. This is currently not available on the NHS and I have not been

involved in its use previously. Etelcalcetide would only be licensed for use in haemodialysis patients and therefore would only be used in secondary and tertiary services where haemodialysis is offered. This should only be prescribed by nephrologists who have experience in managing secondary hyperparathyroidism. For this medicine to be administered the dialysis unit nursing staff would need to be educated in the handling and administration of Etelcalcetide.

The advantages and disadvantages of the technology

Etelcalcetide is an alternative to Cinacalcet HCl for the management of Secondary and Tertiary hyperparathyroidism. Haemodialysis patients have a very high tablet burden and one the main issues in patient management is medication adherence. As this medication would be given during each dialysis session the adherence and therefore medication exposure is likely to be substantially greater than when taking oral medication. This medicine needs to be administered during the 'wash-back' of the patient at the end of the dialysis session or immediately after wash-back followed by an intravenous flush. Haemodialysis units in the UK are usually organised with set 'shifts' for the patients to attend and therefore there are busy 'change-over' times within a dialysis unit. The administration of this would have to take place during this busy time and may add more stress into the system. However it is likely that the number of patients requiring this medication will be a minority and therefore this may have limited impact.

When a dose is adjusted extra blood tests are required. Blood tests are regularly performed in a haemodialysis unit as these can be done as the patient is commenced on treatment but also occurs during 'change-over'. The laboratory would also need to support the extra sampling.

The side effect profile with Cinacalcet HCl can limit the dose a patient can tolerate; the similar profile suggests no immediate benefit for Etelcalcetide. The trials suggest Etelcalcetide had a superior effect to Cinacalcet HCl and this maybe useful if patients are unable to tolerate a higher dose of Cinacalcet HCl. The side effects can affect quality of life but sometimes the cause settles with time or prescribe the maximum tolerated dose to aid the patients management.

Patients who transfer renal replacement modality during their renal career would not be able to continue on this medication due to its route of administration. This may occur if a patient transfers to peritoneal dialysis or has a renal transplant. If the patient is commenced on this medication this would need to be explained to the patient in advance.

I feel that the rules used within the trials are appropriate for starting and stopping the medication especially with respect to hypocalcaemia. These rules include the minimum calcium level at commencement, the dose changes suggested if a low calcium is discovered and the frequency of blood tests after dose changes. These are similar to the rules used for Cinacalcet HCl and therefore do not represent a difference in practice.

The clinical trials included adults on haemodialysis with PTH > 400 or 500 pg/ml; the maximum recommended PTH level, according to KDIGO in 2009 is about 580pg/ml (depending on the assay used) therefore these patients are approaching the upper

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

end of our target range. The trials showed a substantial proportion (about 70%) of patients on Etelcalcetide achieving >30% drop in the PTH levels and more than 50% less than 300pg/ml. This is difficult to achieve with the current medications we have available in clinical practice. The trial definitions are different to the current guidance for the use of Cinacalcet HCl. By allowing the PTH to increase to 800 pg/ml before starting calcimimetic treatment the gland may have become less responsive and therefore more likely to fail treatment. Therefore in 'real world' use this may not produce as good results, depending on what restrictions are placed if approved.

The mean age in the clinical trials are lower than we would see in our general dialysis population as more patients are commencing dialysis at an older age compared to previous. The effects of secondary hyperparathyroidism affect the elderly more due to their general frailty and therefore they may have the greatest benefits from the positive effects of this medication.

The main outcomes of the trial are the percentage change in PTH which is a surrogate biochemical marker. High levels of PTH have been associated with increased mortality though this varies between >400-600 pg/ml.

The trials have shown a reduction in CTX which is a marker for bone resorption. This is an encouraging result and suggests that Etelcalcetide may also improve bone histomorphometry (Cinacalcet HCl showed this in the BONAFIDE study). FGF23 levels have also reduced in the study with Etelcalcetide treatment and this may also impact on mortality.

The most important outcomes that need to be measured in renal patients would include mortality, cardiovascular end-points, and other secondary endpoints such as FGF23, Left ventricular hypertrophy and vascular calcification. The trials performed have shown a reduction in FGF23 but a specific RCT evaluating the reduction of FGF23 as an outcome could be considered.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

I do not foresee that this treatment would exclude any people

- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

I do not foresee that this treatment would exclude any groups

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

I do not foresee an adverse impact on people with any disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I cannot offer any other information

Implementation issues

Etelcalcetide would be beneficial to be able to manage the patients with severe secondary or tertiary hyperparathyroidism. The potential benefits include:

- Reduction in mortality with the reduction in PTH and FGF23
- Improvement in bone health as CTX fell suggesting bone turnover better controlled. This could impact fracture risk and hospitalisation rate
- Improvement in quality of life - no bone pain associated with secondary hyperparathyroidism.

This care can be delivered in the current design of haemodialysis care in the UK. Nurses would need to be educated on how and when to administer the medication to ensure at the end of the the treatment. There would also be more blood samples to be taken and processed but these would be an extra Calcium and PTH sample per month until the patient reached a steady state. Then the routine blood tests haemodialysis patients already undergo will be sufficient.

Fridge space would be needed to store the medication though all units will have a fridge on site already due to other necessary medications.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Kidney Research UK and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed:

Date: 30/01/2017

CONFIDENTIAL UNTIL PUBLISHED

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

Etelcalcetide for treating secondary hyperparathyroidism

ERRATUM

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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

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

Date completed 11 January 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/10/01.

Acknowledgements

We are very grateful to Dr Kristin Veighey, Consultant Nephrologist Wessex Kidney Centre, Portsmouth, and Clinical Research Physician, University Hospitals Southampton NHS Foundation Trust, who provided clinical advice and commented on a draft of this report. We would also like to thank: Karen Welch, Information Scientist, SHTAC, for appraising the literature search strategies in the company's submission, running updates of the company's clinical effectiveness searches and searching for ongoing studies; and Emma Loveman and Jill Colquitt, Senior Reviewers / Partners, Effective Evidence LLP, for acting as internal editor of the ERG report.

Declared competing interests of the authors

None from the authors. The consultant nephrologist who advised the ERG declared she had no conflicts of interest.

Rider on responsibility for report

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

This report should be referenced as follows:

Pickett K, Lord J, Rose M, Shepherd J, Harris, P. Etelcalcetide for treating secondary hyperparathyroidism: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2016.

Contributions of authors

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

Word count: 50,559

Key to colour highlighting used in report

Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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

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

SUMMARY

Scope of the company submission

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

Summary of submitted clinical effectiveness evidence

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

The systematic review identified and included the following evidence:

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

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

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

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

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

Summary of submitted cost effectiveness evidence

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

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

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

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

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

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

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

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

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

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

Table 1 Company base case cost effectiveness results

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

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

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

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

Commentary on the robustness of submitted evidence

Strengths

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

Weaknesses and areas of uncertainty

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

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

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

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

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

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

Summary of additional work undertaken by the ERG

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

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

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

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

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

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

Table 2 ERG base case: incremental analysis with sequenced strategies

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

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

1 Introduction to ERG Report

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

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

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

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

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

2.2 Critique of company's overview of current service provision

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

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

Treatment initiation and PTH target

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

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

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

Current clinical practice

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

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

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

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

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

Proposed place of etelcalcetide in the clinical pathway

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

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

Potential impact of etelcalcetide on current service provision

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

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

Summary

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

2.3 Critique of company's definition of decision problem

Population

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

Intervention

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

Comparators

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

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

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

Outcomes

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

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

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

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

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

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

Economic analysis

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

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

Other relevant factors

Subgroups

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

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

Equality issues

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

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports two systematic literature searches [redacted]:

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

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

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

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

[redacted] The results were checked by one researcher.

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

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

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

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

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

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

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

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

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

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

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

3.1.3 Identified studies

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

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

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

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

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

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

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

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

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

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

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

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

Table 3 Trial characteristics

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

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

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

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

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

Table 4 Summary of trial outcomes and statistical aspects

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

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

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

Baseline characteristics

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

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

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

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

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

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

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

Table 5 Baseline characteristics of patients in the etelcalcetide RCTs

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

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

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

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

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

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

Non-randomised trials

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

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

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

Summary

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

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

3.1.4 Description and critique of the approach to validity assessment

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

Table 6 Company and ERG assessment of trial quality

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

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

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

3.1.5 Description and critique of company's outcome selection

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

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

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

- adverse effects of treatment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ITT analysis and other analysis sets

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

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

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

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

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

Subgroups

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

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

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

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

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

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

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

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

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

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

3.2 Summary statement of company's approach

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

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

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

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

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

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

3.3 Summary of submitted evidence

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

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

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

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

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

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

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

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

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

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

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

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

[a] Calculated by the ERG.

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

[c] [redacted]

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

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

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

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

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

Table 9 Results for other serum PTH outcomes

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

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

[a] Pooled results from studies 20120229 and 20120230.

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

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

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

3.3.4 Summary of Health related quality of life

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

Table 10 Results for serum calcium and phosphate outcomes

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

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

[a] Pooled results from studies 20120229 and 20120230.

[b] Etelcalcetide:cinacalcet.

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

[d] Missing data imputed using non-responder imputation

[redacted]

[redacted]

Table from company's clarification response.

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

3.3.5 Sub-group analyses results

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

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

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

[redacted]

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

[redacted]

[redacted]

3.3.6 Summary of adverse events

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

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

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

Table 11 Overview of incidence of adverse events in etelcalcetide RCTs

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

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

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

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

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

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

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

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

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

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

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

3.3.7 Summary of non-randomised studies

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

The switch study (20120359)

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

The long-term extension studies (20120231 and 20130213)

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

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

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

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

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

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

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

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

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

3.4 Summary of clinical effectiveness

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

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

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

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

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

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

3.5 Additional cinacalcet evidence

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

3.5.1 Quality assessment of the EVOLVE trial

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

Table 14 Company and ERG assessment of the EVOLVE trial

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

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

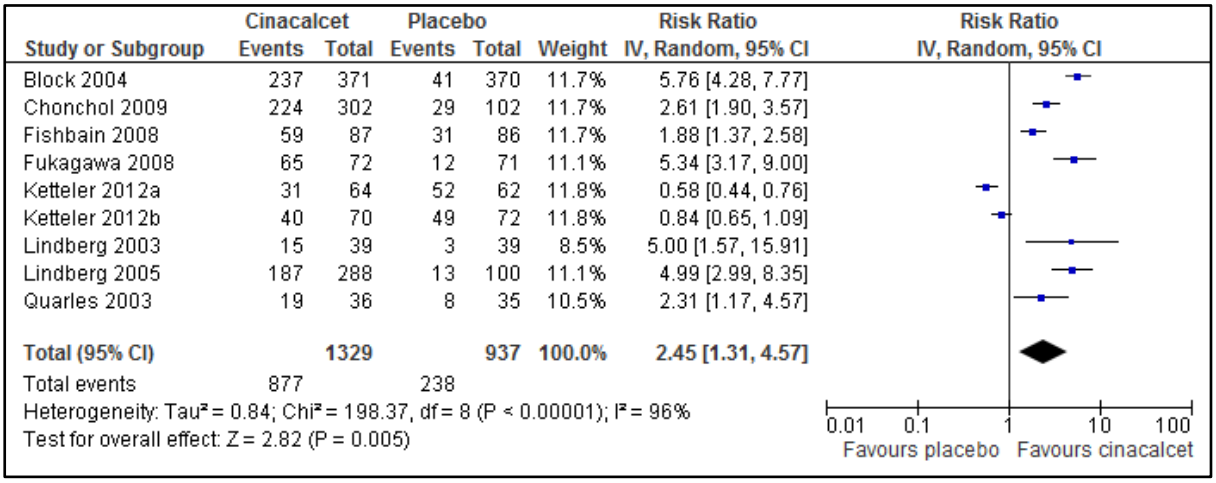
Bias	Domain	CS comments:	CS	ERG	ERG comments:
		High levels of use of commercial cinacalcet in placebo arm.			cinacalcet before the occurrence of a primary event (CS p. 33). The CS implies these factors may have biased findings unfavourably for cinacalcet (CS p. 33 and CS Appendix 4, pp. 54 to 55).
Summary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

3.5.2 ERG meta-analysis of cinacalcet trials

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

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

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



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

Figure 1 – Meta-analysis of cinacalcet studies

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

4 COST EFFECTIVENESS

4.1 Overview of economic evidence

The company's submission to NICE includes:

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

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

4.2 Company's review of published economic evaluations

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

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

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

Table 15 Inclusion criteria for systematic review of economic evaluations

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

Reproduced from CS Table 27, page 84.

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

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

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

4.3 Company's submitted economic model

4.3.1 The reference case

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

Table 16 NICE reference case requirements

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

4.3.2 The decision problem

4.3.2.1 Base case population

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

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

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

Table 17. Baseline characteristics of participants in main clinical trials

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

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

Source: Adapted from Table 14 CS page 58.

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

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

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

4.3.2.2 Subgroup analysis

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

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

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

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

4.3.2.3 Intervention and comparators

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

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

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

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

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

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

4.3.3 Model structure and assumptions

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

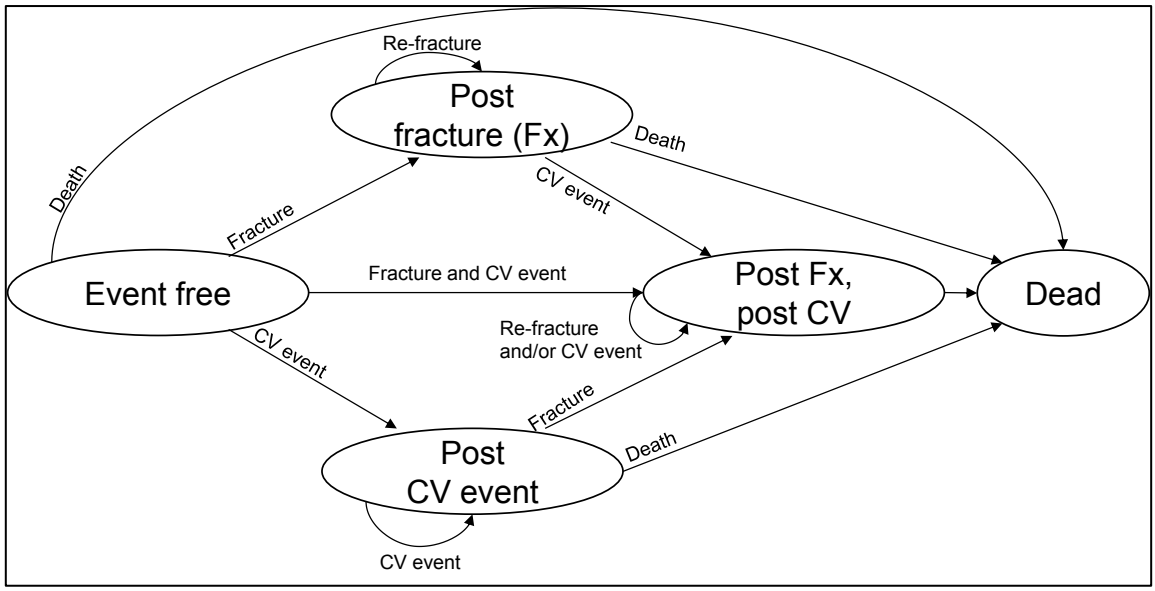


Figure 2. Basic Markov model structure
Reproduced from CS 5.2.2 Page 91

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

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

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

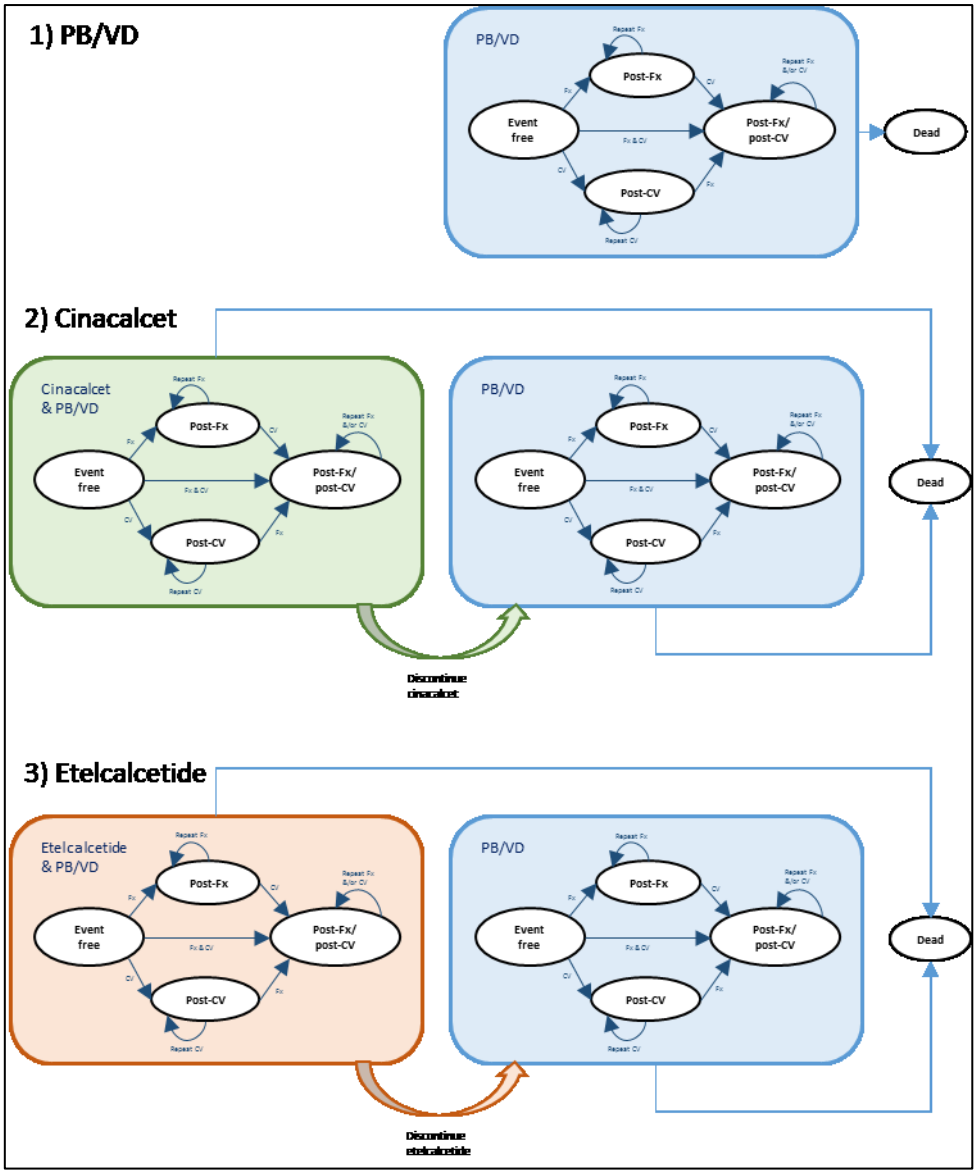


Figure 3. Treatment strategies modelled in CS

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

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

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

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

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

4.3.4 Methods to estimate effects

4.3.4.1 Overview

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

Table 18. Methods to estimate treatment effects

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

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

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

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

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

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

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

4.3.4.2 EVOLVE estimates of cinacalcet hazard ratios

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

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

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

Table 19 EVOLVE hazard ratios with adjustments for non-adherence

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

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

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

2. CS Table 33. Results adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

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

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

Method A) Lag-censored analysis

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

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

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

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

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

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

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

Method B) ITT persistence disaggregated

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

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

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

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

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

Method D) Iterative Parameter Estimation (IPE)

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

4.3.4.3 Extrapolation of EVOLVE efficacy to etelcalcetide

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

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

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

(CS Table 32, p. 97)

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

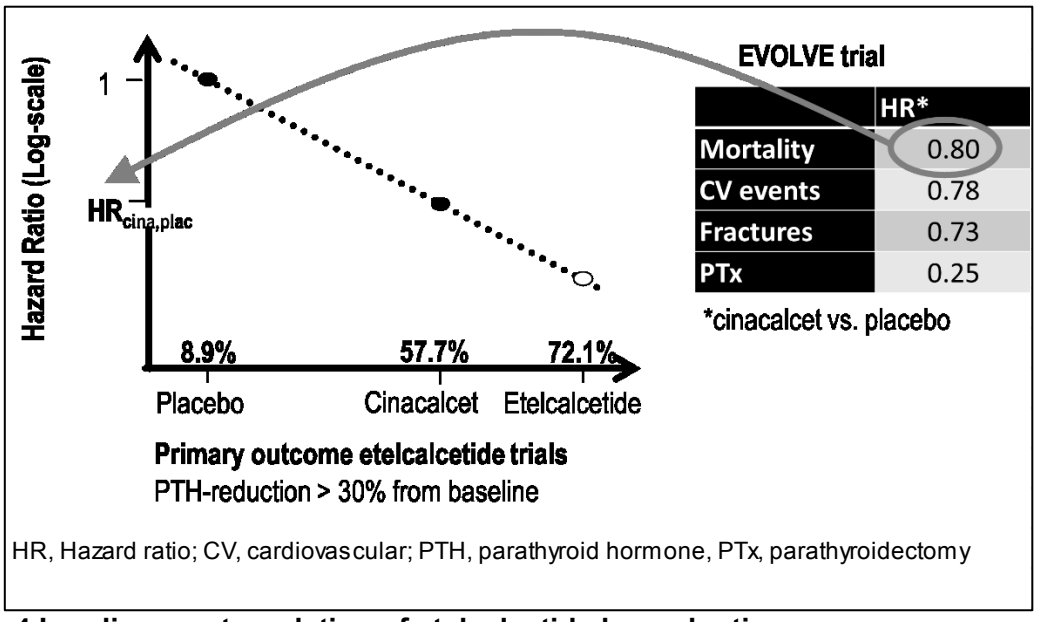


Figure 4 Log-linear extrapolation of etelcalcetide hazard ratios
(CS Figure 15, p. 98)

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

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

Source: Stollenwerk et al.2016 [22]

1. Myocardial infarction, unstable angina, heart failure and peripheral vascular event
2. Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials
3. Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

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

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

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

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

1. Myocardial infarction, unstable angina, heart failure and peripheral vascular event
2. Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials
3. Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin

4.3.4.4 Eandi et al. risk prediction scheme

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

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

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

CV, cardiovascular; HR, hazard ratio

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

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

4.3.4.5 ERG conclusions on methods for modelling treatment effects

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

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

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

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

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

4.3.5 Input parameters

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

Table 24 Summary of sources used to inform model parameters

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

4.3.5.1 Background event rates

All-cause mortality

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

Table 25 Background mortality rates used in the economic model

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

Source: CS Table 38, p. 102

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

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

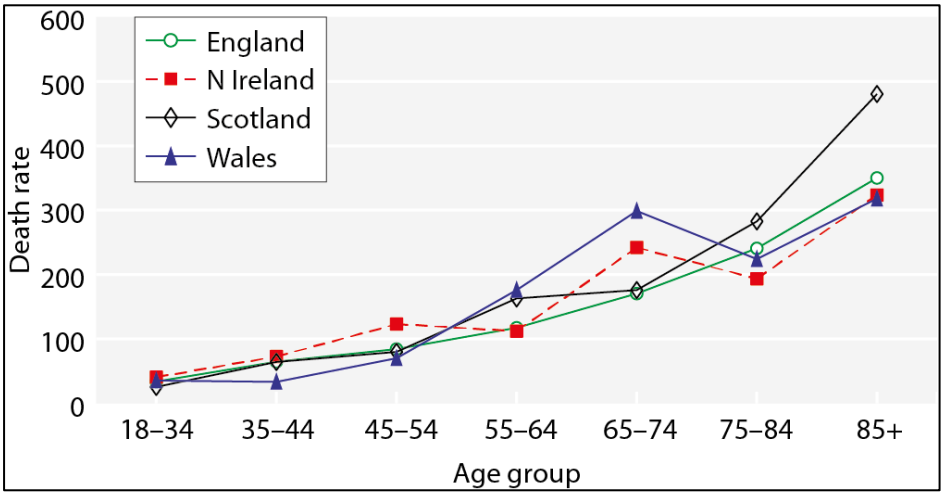


Figure 5. One year death rate per 1,000 patient years by UK country and age group for prevalent dialysis patients, 2013 cohort

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

Other event rates

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

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

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

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

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

CV, cardiovascular

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

From CS Table 39, page 103

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

4.3.5.2 Treatment effects

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

Table 27. Estimated hazard ratios used in company model

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

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

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

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

4.3.5.3 Treatment discontinuation

Cinacalcet discontinuation

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

Table 28 One-year calcimimetic persistence data

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

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

Etelcalcetide discontinuation

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

Table 29 Discontinuation of etelcalcetide and cinacalcet in 20120360

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

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

4.3.5.4 Health related quality of life

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

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

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

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

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

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

Table 30 Utility estimates used in the decision-analytic model

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

(CS Table 45, p. 111)

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

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

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

Adverse events

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

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

4.3.5.5 Resource use and costs

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

Table 31 Summary of cost of illness studies

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

MPR Medication Possession Ratio; PTH parathyroid hormone; PTx parathyroidectomy; SHPT secondary hyperparathyroidism
GBP Great Britain Pounds Sterling; USD United States Dollars; EUR Euros
(CS Table 46, p. 112)

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

Drug acquisition costs

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

Table 32 Calcimimetic drug consumption from the etelcalcetide trials

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

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

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

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

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

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

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

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

Drug costs

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

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

Table 34 Average drug cost per unit used in the model

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

(CS Table 49, p. 114-115)

Event costs

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

Table 35 Event costs

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

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

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

Monitoring costs

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

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

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

Dialysis costs

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

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

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

4.3.6 Model validation

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

4.3.6.1 Internal consistency

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

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

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

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

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

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

- Checking visual basic coding

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

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

4.3.6.2 External consistency

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

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

4.3.7 Cost effectiveness results

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

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

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

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

4.3.8 Assessment of uncertainty

Deterministic sensitivity analyses

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

Table 39 Ranges used for deterministic sensitivity analyses

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

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

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

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

Figure 6

Figure 7

Scenario analysis

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

Table 40 Summary of company base case and scenario analyses

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

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

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

Table 41 Scenario analysis: base case with anticipated list price

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

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

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

Probabilistic sensitivity analysis

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

Table 42 Summary of distributions for probabilistic analysis

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

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

4.4 Additional work undertaken by the ERG

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

4.4.1 Additional scenario analyses

4.4.1.1 Efficacy of SHPT control: 30% reduction in PTH

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

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

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

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

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

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

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

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

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

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

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

We draw the following conclusions from this analysis.

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

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

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

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

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

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

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

4.4.1.3 Method of extrapolation

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

We conclude:

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

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

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

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

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

4.4.1.4 Discontinuation of etelcalcetide and cinacalcet

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

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

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

Table 47 Scenario analysis by discontinuation assumptions: anticipated list price

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

HR hazard ratio

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

4.4.1.5 Utility benefits of calcimimetics

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

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

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

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

E etelcalcetide; C cinacalcet

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

4.4.1.6 Sequencing of calcimimetics

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

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

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

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

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

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

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

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

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

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

4.4.2 Additional subgroup analyses

4.4.2.1 Propensity for SHPT control on PB/VD alone

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

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

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

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

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

ITC indirect treatment comparison; PTH parathyroid hormone

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

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

4.4.2.2 Patients with previous events

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

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

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

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

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

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

4.4.3 ERG preferred analysis

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

4.4.3.1 ERG base case

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

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

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

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

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

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

Table 53 ERG base case: anticipated list price

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

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

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

4.4.3.2 ERG subgroup analysis

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

Table 54 ERG subgroup analysis: anticipated list price

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

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

4.4.3.3 ERG analysis with sequenced calcimimetics

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

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

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

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

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

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

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

4.4.3.4 ERG assessment of uncertainty

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

4.5 Summary

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

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

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

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

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

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

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

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

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

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

5 End of life

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

6 Innovation

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

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

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

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

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

7.2 Summary of cost effectiveness issues

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

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

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

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

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

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

8 REFERENCES

1. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clinical Journal of the American Society of Nephrology 2011;**6**:913.
2. Garside R, Pitt M, Anderson R, et al. The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation. Health Technology Assessment 2007;**11**(18).
3. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Supplement to Kidney International 2009;**76**(Supplement 113):S121-S30.
4. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management (CG 182): NICE, 2014.
5. National Institute for Health and Care Excellence. Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia (CG 157): NICE, 2013.
6. National Institute for Health and Care Excellence. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. Technology appraisal guidance [TA117], 2007.
7. Steddon S, Sharples E. UK Renal Association clinical practice guideline: CKD-mineral and bone disorders (CKD-MBD): UK Renal Association, 2015.
8. Uhlig K, Berns JS, Kestenbaum B, et al. KDOQI US commentary on the 2009 KDIGO clinical practice guidelines for the diagnosis, evaluation, and treatment of CKD-mineral and bone disorder (CKD-MBD). American Journal of Kidney Diseases 2010;**55**(5):773-99.
9. Hedgeman E, Lipworth L, Lowe K, et al. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. International Journal of Nephrology 2015;**2015**(Article ID 184321).
10. Bushinsky DA, Block GA, Martin KJ, et al. Treatment of Secondary Hyperparathyroidism: Results of a Phase 2 Trial Evaluating an Intravenous Peptide Agonist of the Calcium-Sensing Receptor. American Journal of Nephrology 2015;**42**(5):379-88.
11. European Medicines Agency. CHMP Assessment Report: Parsabiv (draft), 2016.
12. Amgen. 20120229 Clinical Study Report, 2014.
13. Amgen. 20120230 Clinical Study Report, 2014.
14. Amgen. 20120360 Clinical Study Report, 2015.
15. Amgen. AMG 416 Summary of Clinical Efficacy. 2015.
16. Bushinsky D, Block G, Cheng S, et al. One Year Efficacy and Safety of Intravenous Etelcalcetide (AMG 416) in Patients on Hemodialysis with Secondary Hyperparathyroidism (Study 20120231). 53rd ERA-EDTA Congress, 21-24 May 2016. Vienna, Austria., 2016.
17. Amgen data on file. Study 20130213 Interim analysis summary 2016. 2016.
18. Chertow GM, Block GA, Correa-Rotter R, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. The New England Journal Of Medicine 2012;**367**(26):2482-94.
19. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd.: CRD, 2009.
20. Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. Clinical Journal of the American Society of Nephrology : CJASN 2015;**10**(1):98-109.
21. Ballinger AE, Palmer SC, Nistor I, et al. Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients. The Cochrane Database of Systematic Reviews 2014(12):Cd006254.

22. Stollenwerk B, Dehmel B, Akehurst R, et al. Modelling etelcalcetide effectiveness on health outcomes: Relating biochemical outcomes to mortality, cardiovascular events, fractures and parathyroidectomy. Presented at: Society for Medical Decision Making (SMDM), 16th Biennial European Conference, London; June 14, 2016. 2016.
23. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013. NICE, London, 2013.
24. Amgen. AMG 416 Summary of Clinical Safety. 2015.
25. Amgen. 20120360 Clinical Study Report. 2015.
26. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011.
27. Parfrey PS, Chertow GM, Block GA, et al. The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: the EVOLVE trial. The Journal of clinical endocrinology and metabolism 2013;**98**(12):4834-44.
28. Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;**350**(15):1516-25.
29. Fishbane S, Shapiro WB, Corry DB, et al. Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. Clinical Journal of the American Society of Nephrology : CJASN 2008;**3**(6):1718-25.
30. Chonchol M, Locatelli F, Abboud HE, et al. A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Participants With CKD Not Receiving Dialysis. American Journal of Kidney Diseases 2009;**53**(2):197-207.
31. Fukagawa M, Yumita S, Akizawa T, et al. Cinacalcet (KRN1493) effectively decreases the serum intact PTH level with favorable control of the serum phosphorus and calcium levels in Japanese dialysis patients. Nephrol Dial Transplant 2008;**23**(1):328-35.
32. Ketteler M, Martin KJ, Wolf M, et al. Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study. Nephrology Dialysis Transplantation 2012.
33. Lindberg JS, Culleton B, Wong G, 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. Journal of the American Society of Nephrology : JASN 2005;**16**(3):800-7.
34. Lindberg JS, Moe SM, Goodman WG, et al. The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism. Kidney Int 2003;**63**(1):248-54.
35. Quarles LD, Sherrard DJ, Adler S, et al. The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. Journal of the American Society of Nephrology : JASN 2003;**14**(3):575-83.
36. Belozeroff V, Chertow GM, Graham CN, et al. Economic Evaluation of Cinacalcet in the United States: The EVOLVE Trial. Value In Health 2015;**18**(8):1079-87.
37. Eandi M, Pradelli L, Iannazzo S, et al. Economic evaluation of cinacalcet in the treatment of secondary hyperparathyroidism in Italy. Pharmacoeconomics 2010;**28**(11):1041-54.
38. Amgen. EVOLVE Clinical Study Report, 2013.
39. Belozeroff V, Cooper K, Hess G, et al. Healthcare use and costs before and after parathyroidectomy in patients on dialysis. BMC Health Services Research 2013;**13**(1):1.
40. Parfrey PS, Block GA, Correa-Rotter R, et al. Lessons learned from EVOLVE for planning of future randomized trials in patients on dialysis. Clinical Journal of the American Society of Nephrology 2015:CJN. 06370615.

41. Latimer NR, Abrams KR, Lambert PC, et al. Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: methods, limitations, and recommendations. Medical Decision Making: An International Journal Of The Society For Medical Decision Making 2014;**34**(3):387-402.
42. Kubo Y, Sterling LR, Parfrey PS, et al. Assessing the treatment effect in a randomized controlled trial with extensive non-adherence: the EVOLVE trial. Pharm Stat 2015;**14**(3):242-51.
43. Tripepi G, Heinze G, Jager KJ, et al. Lag-censoring analysis: lights and shades. Nephrol Dial Transplant 2015;**30**(5):700-5.
44. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching, 2014.
45. Boer R, Lalla AM, Belozeroff V. Cost-effectiveness of cinacalcet in secondary hyperparathyroidism in the United States. J Med Econ 2012;**15**(3):509-20.
46. Reams B, Dluzniewski P, Do T, et al. Dynamics of cinacalcet use and biochemical control in hemodialysis patients: A Retrospective New-User Cohort Design. BMC Nephrology 2015;**16**:175.
47. Urena P, Jacobson SH, Zitt E, et al. Cinacalcet and achievement of the NKF/K-DOQI recommended target values for bone and mineral metabolism in real-world clinical practice--the ECHO observational study. Nephrol Dial Transplant 2009;**24**(9):2852-9.
48. Briggs AH, Parfrey PS, Khan N, et al. Analyzing Health-Related Quality of Life in the EVOLVE Trial: The Joint Impact of Treatment and Clinical Events. Med Decis Making 2016;**36**(8):965-72.
49. Joint Formulary Committee. *British National Formulary*: London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2016.
50. NHS Business Services Authority. NHS Electronic Drug Tariff. Available from: http://www.drugtariff.nhsbsa.nhs.uk/, 2016.
51. Department of Health. NHS reference costs 2014-15. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/480791/2014-15_National_Schedules.xlsx: Department of Health, England, UK, 2015.
52. Pockett RD, Cevro E, Scott-Coombes D, et al. Assessment of the Resource Use and Costs Associated with Parathyroidectomy Surgery for Secondary Hyperparathyroidism in End Stage Renal Disease in the UK - poster. ISPOR 2012.
53. Amgen. Baseline mortality rates. Data on file, 2016.
54. Steenkamp R, Rao A, Fraser S. UK Renal Registry 18th Annual Report (December 2015) Chapter 5: Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2014: National and Centre-specific Analyses. Nephron 2016;**132(suppl 1)**(Suppl. 1):111-44.
55. Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. Journal of the American Society of Nephrology 2004;**15**(8):2208-18.
56. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention 2003;**108**(17):2154-69.
57. Malindretos P, Sarafidis P, Lazaridis A, et al. A study of the association of higher parathormone levels with health-related quality of life in hemodialysis patients. Clinical Nephrology 2012;**77**(03):196-203.
58. Filipozzi P, Ayav C, Erpelding ML, et al. Influence on quality of life from an early cinacalcet prescription for secondary hyperparathyroidism in dialysis. Pharmacoepidemiol Drug Saf 2015;**24**(2):187-96.
59. Lun L, Li X, Wei X, et al. Effects of parathyroidectomy on quality of life in uremic patients with secondary hyperparathyroidism. Presented at 51st ERA-EDTA Congress; 31 May- 3 June 2014; Amsterdam, Netherlands. Nephrol Dial Transplant 2014;**29**:iii270.

60. Davies E, Matza L, Worth G, et al. Impact of Major Clinical Events on Utilities in the Context of Secondary Hyperparathyroidism (SHPT) and Chronic Kidney Disease (CKD) Treated with Dialysis. 2013.
61. Duenas A FJ, Rawdin A, Wilkie M, Harrison B, Akehurst R. Assessing the cost of parathyroidectomy as a treatment for uncontrolled secondary hyperparathyroidism in stage 5 chronic kidney disease. Paper presented at 17th ERA-EDTA Congress - II DGfN Congress; 25-28 June 2010; Munich, Germany NDT Plus 2010;3(iii98-iii99) 2010.
62. Schumock GT WS, Lee TA, Marx SE, Audhya P, Andress DL. Comparative effectiveness of paricalcitol versus cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. Nephron 2011;117(2):c151-9 2011.
63. Lee A, Song X, Belozeroff V, et al. Costs of Care and Major Clinical Events Among Chronic Dialysis Patients With and Without Treatment for SHPT: A Descriptive Study of Claims Data - poster. ASN 2011.
64. Chiroli S, Mattin C, Belozeroff V, et al. Impact of mineral and bone disorder on healthcare resource use and associated costs in the European Fresenius medical care dialysis population: a retrospective cohort study. BMC Nephrology 2012;**13**:140.
65. Lee A, Belozeroff V, Song X, et al. Costs of Treatment and Clinical Events for Secondary Hyperparathyroidism. Am J Pharm Benefits 2013;**5**(2):e24-e35.
66. Pockett RD, Cevro E, Chamberlain G, et al. Assessment of Resource Use and Costs Associated with Parathyroidectomy for Secondary Hyperparathyroidism in End Stage Renal Disease in the UK. Journal of medical economics 2014;**17**(198-206).
67. Amgen. Average Dose of Calcimimetic Drugs during the Efficacy Assessment Phase. Data on file., 2016.
68. Amgen. Use of Active Vitamin D – pooled. Data on File. 2016.
69. Health & Social Care Information Centre. Prescription Cost Analysis England 2015. Available from: http://www.hscic.gov.uk/catalogue/PUB20200., 2015.
70. Curtis L. Unit Costs of Health and Social Care 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php?file=full: Personal Social Services Research Unit, 2015.
71. Amgen. Frequency and Type of Dialysis. Data on file., 2016.
72. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;**26**(4):404-13.
73. Briggs A, Parfrey P, Khan N, et al. Analyzing Health-Related Quality of Life in the EVOLVE Trial: The Joint Impact of Treatment and Clinical Events. Med Decis Making 2016: pii: 0272989X16638312. [Epub ahead of print].
74. Garside R, Pitt M, Anderson R, et al. The cost-utility of cinacalcet in addition to standard care compared to standard care alone for secondary hyperparathyroidism in end-stage renal disease: a UK perspective. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2007;**22**(5):1428-36.
75. Latimer NR, Abrams K, Lambert P, et al. Adjusting for treatment switching in randomised controlled trials - A simulation study and a simplified two-stage method. Stat Methods Med Res 2014.

9 APPENDICES

ERG Scenario analyses

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

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

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

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

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

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

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

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

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

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

* ICER for cina-etel compared with etel-cina

CONFIDENTIAL UNTIL PUBLISHED

Etelcalcetide for treating secondary hyperparathyroidism

Confidential addendum to Evidence Review Group report

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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

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

Date completed 31 January 2017

1 Introduction

Amgen submitted a Patient Access Scheme (PAS) to NICE on 25th January 2017. This addendum to the ERG report presents the results of the ERG check on the impact of the proposed PAS on the cost-effectiveness of etelcalcetide for the treatment of secondary hyperparathyroidism. We attempted to replicate the company's analyses from their PAS submission, and also repeated the additional ERG analyses presented in our main report.

2 Details of the PAS scheme

The proposed PAS is a simple confidential discount on the NHS list price for etelcalcetide of each vial size (see Table 1). We confirm that the reported PAS prices do represent a [redacted] reduction on the reported NHS list price.

Table 1. NHS list price and PAS price for etelcalcetide

Dose (mg)		2.5 mg	5 mg	10 mg
Pack size (vials)		6	6	6
NHS list price	per pack	[redacted]	[redacted]	[redacted]
	per vial	[redacted]	[redacted]	[redacted]
	per mg	[redacted]	[redacted]	[redacted]
PAS price	per pack	[redacted]	[redacted]	[redacted]
	per vial	[redacted]	[redacted]	[redacted]
	per mg	[redacted]	[redacted]	[redacted]
	% reduction	[redacted]	[redacted]	[redacted]

The company reported a weighted average cost at list price ([redacted] per mg) and at PAS price ([redacted] per mg), based on the distribution of vial usage in the three etelcalcetide trials (20120229, 20120230 and 20120360). The estimated cost at the confirmed NHS list price is higher than the anticipated cost in the company submission ([redacted] per mg). The PAS submission therefore presented revised cost-effectiveness results for the NHS list price, as well as for the PAS.

The frequency of dose administration was calculated during the efficacy assessment phase (EAP) of the trials, using the pooled, safety analysis set, which includes all patients who received at least one non-missing dose of etelcalcetide and excludes patients who received commercial cinacalcet. The company stated that three doses were recorded incorrectly (two as 9 mg and one as 9.5 mg), but that these cases were excluded from the price calculations. However, we note that the percentage

distribution of vial doses reported in the PAS submission includes these three cases, with the assumption that they received a 10mg dose. This is a reasonable assumption with little impact on the estimated weighted price.

The dose and vial usage reported in the PAS submission are shown in Table 2. In total, 11,743 doses were administered, between a minimum of 2.5 mg and maximum of 15 mg. The company estimated the distribution of vial usage by assuming use of the minimum number of vials, with no sharing of vials. Based on these data and assumptions, we confirm the company's estimates of the mean cost per mg of etelcalcetide at the NHS list prices and at the PAS prices.

Table 2. Distribution of dose and estimated vial usage

Dose	Frequency	2.5 mg	5 mg	10 mg
2.5 mg	[redacted]	[redacted]		
5.0 mg	[redacted]		[redacted]	
7.5 mg	[redacted]	[redacted]	[redacted]	
10.0 mg	[redacted]			[redacted]
12.5 mg	[redacted]	[redacted]		[redacted]
15.0 mg	[redacted]		[redacted]	[redacted]
Estimated number of vials		[redacted]	[redacted]	[redacted]
Estimated vial distribution		[redacted]	[redacted]	[redacted]

Subjects enrolled in studies 20120229 and 20120230, and 20120360 randomised to receive etelcalcetide.
Safety analysis set: all subjects in the pool who received at least one non-missing dose of etelcalcetide and exclude subjects who received commercial use of cinacalcet.
Dose assumed to be given using the minimum number of vials.
Three doses were recorded erroneously (1 instance of 9 mg and 2 instances of 9.5 mg), assumed to receive 10mg dose

In summary, estimates of the cost per mg for etelcalcetide are shown in Table 3.

Table 3. Estimated cost per mg for etelcalcetide

	Cost per mg
Anticipated list price in Company Submission	[redacted]
Confirmed NHS list (PAS Submission)	[redacted]
Proposed PAS price (PAS Submission)	[redacted]

3 Base case analysis

Pairwise cost- effectiveness results for the company's base case analysis at the confirmed NHS list price and with the PAS are shown in Table 4. For comparison, we also repeat the results for the anticipated list price that was used in the original company submission. The results that we calculated from the model match those reported in the company's PAS submission.

Table 4 Cost effectiveness results: company base case at different prices

	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Etelcalcetide (with PB/VD) versus PB/VD alone			
Anticipated list price in CS ([redacted] per mg)	[redacted]	0.321	[redacted]
Confirmed NHS list price ([redacted] per mg)	[redacted]	0.321	[redacted]
Proposed PAS price ([redacted] per mg)	£8,738	0.321	£27,251
Etelcalcetide (with PB/VD) versus cinacalcet (with PB/VD)			
Anticipated list price in CS ([redacted] per mg)	[redacted]	0.069	[redacted]
Confirmed NHS list price ([redacted] per mg)	[redacted]	0.069	[redacted]
Proposed PAS price ([redacted] per mg)	£1,020	0.069	£14,777

4 Sensitivity analyses

We re-ran the company's deterministic sensitivity analyses. At list price, the results were similar to those in the original company submission. The hazard ratio for mortality had the greatest impact on the results, but ICERs remained above £30,000 per QALY for all input values tested, for both comparisons. With the PAS, however, the ICERs remained below £30,000 per QALY for all input values tested, except for the higher range of the mortality HR in the etelcalcetide vs. PB/VD comparison (**Error! Reference source not found.**). We note that the tornado diagram for telcalcetide vs. cinacalcet in the PAS submission (Figure 4, page 22) did not include cinacalcet dose. We have added this in Figure 1.

Probabilistic sensitivity analysis around the company base case with the PAS also showed less uncertainty over the cost-effectiveness of etelcalcetide than with the list price estimates. At list prices, the estimated probability that the ICER is below £30,000 per QALY is very close to zero for both comparisons. However, with the PAS, this probability is about 70% for the comparison with PB/VD alone and over 90% for the comparison with cinacalcet (Figure 2).

Figure 1. Tornado diagrams: company base case with PAS

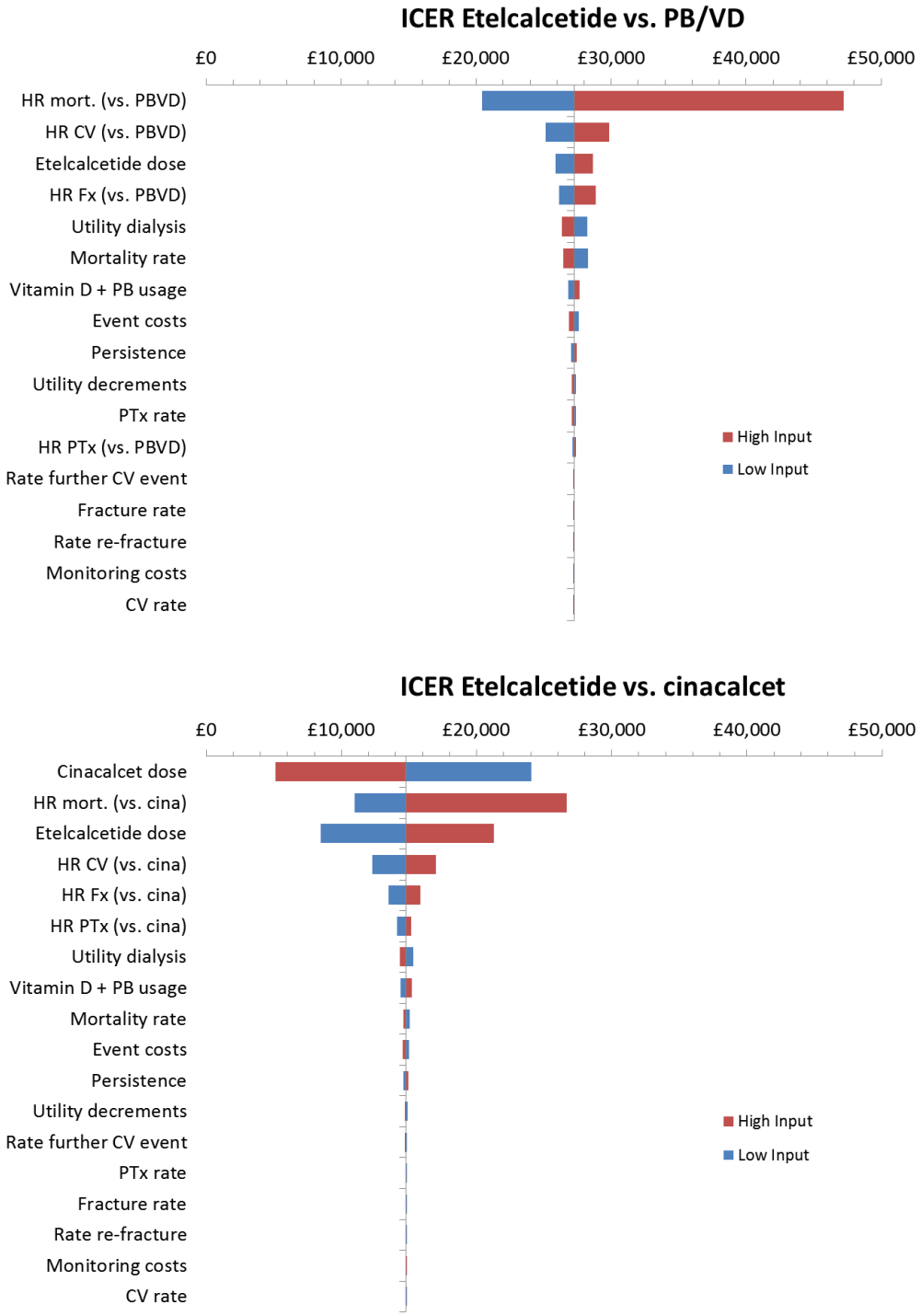
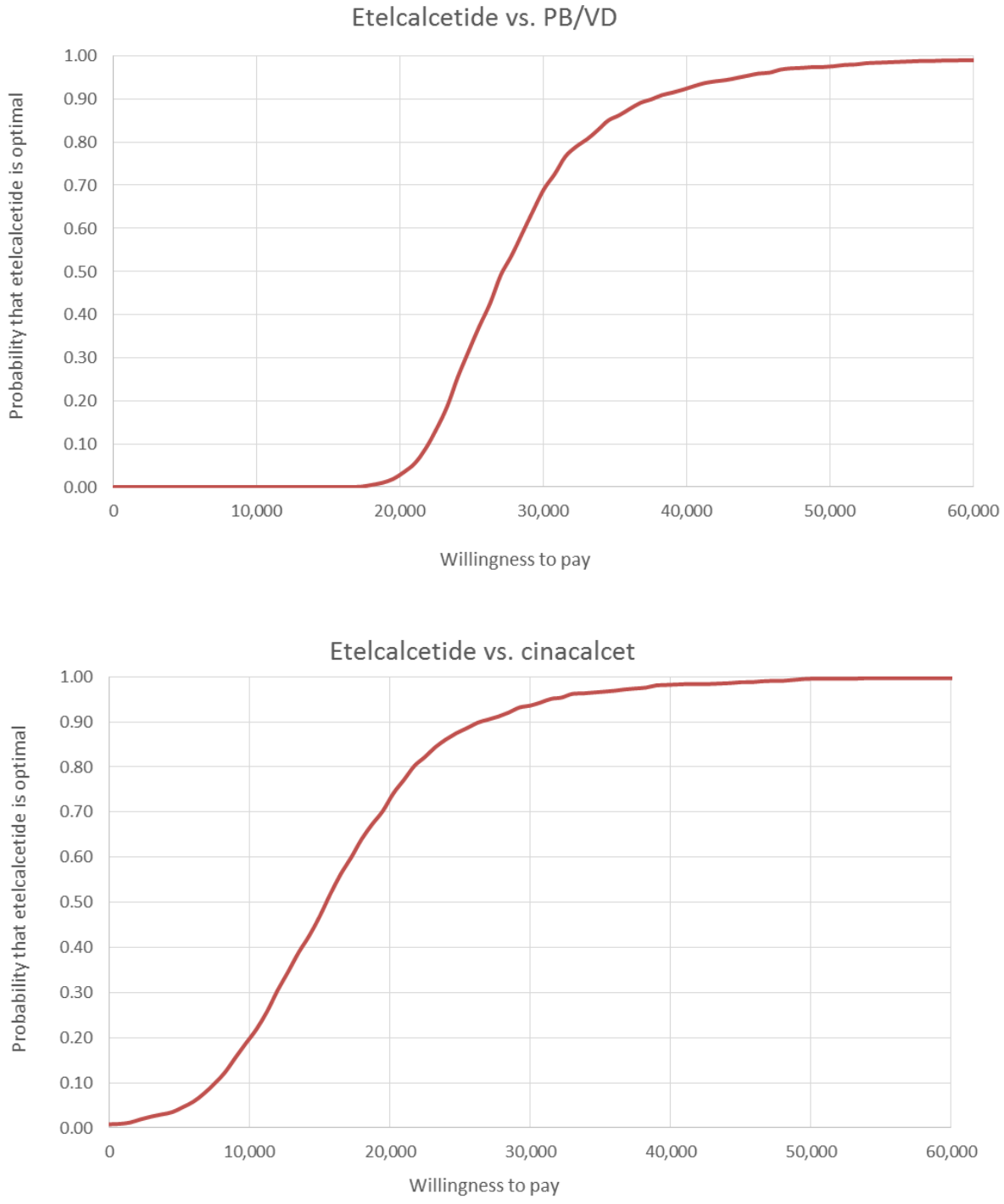


Figure 2. CEACs: company base case with PAS



We also ran the company's scenario analyses with and without the PAS: see Table 5 for the comparison with PB/VD alone and Table 6 for the comparison with cinacalcet. For comparison we

also present the ICERs based on the anticipated list price from the original company submission. At list price, none of the ICERs were below £30,000 per QALY, for either comparison. However, with the PAS the ICERs were less than £30,000 per QALY for almost all of the scenarios tested. The exceptions were:

- the analyses using the Eandi et al risk prediction method to extrapolate trial results in the comparison with PB/VD alone.
- The analyses in which dialysis costs were included, for both comparisons.

Table 5 Company scenario analyses: ICERs for Etelcalcetide vs. PB/VD

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
Company base case	[redacted]	[redacted]	£27,251
Efficacy: EVOLVE ITT disaggregated	[redacted]	[redacted]	£25,453
Efficacy: Eandi; censored	[redacted]	[redacted]	£36,834
Efficacy: Eandi; ITT disaggregated	[redacted]	[redacted]	£31,857
Age at baseline: 45 years	[redacted]	[redacted]	£28,759
Age at baseline: 65 years	[redacted]	[redacted]	£26,159
PTx: not included (rate=0)	[redacted]	[redacted]	£28,525
Mortality: EVOLVE	[redacted]	[redacted]	£27,490
Discontinuation: Reams et al	[redacted]	[redacted]	£25,144
Discontinuation: Urena et al.	[redacted]	[redacted]	£27,592
Utility: Impact calcimimetic treatment	[redacted]	[redacted]	£23,843
Calcimimetic drug use: EAP; head to head	[redacted]	[redacted]	£28,564
Dialysis costs: included	[redacted]	[redacted]	£61,280
Discount rate: 0%	[redacted]	[redacted]	£23,609
Discount rate: 6%	[redacted]	[redacted]	£29,835

Table 6 Company scenario analyses: ICERs for Etelcalcetide vs. cinacalcet

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
Company base case	[redacted]	[redacted]	£14,777
Efficacy: EVOLVE ITT disaggregated	[redacted]	[redacted]	£14,622
Efficacy: Eandi; censored	[redacted]	[redacted]	£19,333
Efficacy: Eandi; ITT disaggregated	[redacted]	[redacted]	£15,974
Age at baseline: 45 years	[redacted]	[redacted]	£15,199
Age at baseline: 65 years	[redacted]	[redacted]	£14,504
PTx: not included (rate=0)	[redacted]	[redacted]	£15,271
Mortality: EVOLVE	[redacted]	[redacted]	£14,962
Discontinuation: Reams et al	[redacted]	[redacted]	£13,707
Discontinuation: Urena et al.	[redacted]	[redacted]	£15,053
Utility: Impact calcimimetic treatment	[redacted]	[redacted]	£14,633
Calcimimetic drug use: EAP; head to head	[redacted]	[redacted]	£20,879
Dialysis costs: included	[redacted]	[redacted]	£48,677
Discount rate: 0%	[redacted]	[redacted]	£13,156
Discount rate: 6%	[redacted]	[redacted]	£15,937

5 Additional ERG analyses

We repeated the additional ERG analyses presented in Section 4.4.1 of the ERG report, using the updated list price and PAS: see Table 7 and Table 8. In all cases the estimated ICERs remained below £30,000 per QALY with the PAS, except for the analysis in which we applied the direct utility benefit estimated from the analysis of EQ-5D data from the EVOLVE trial only to cinacalcet (assuming no direct benefit with etelcalcetide). In this case, the ICER for etelcalcetide compared with cinacalcet was £42,761 with the PAS.

Table 7 ERG additional analyses: ICERs for Etelcalcetide vs. PB/VD

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
Company base case	[redacted]	[redacted]	£27,251
Efficacy: simple ITC etelecalcetide trials	[redacted]	[redacted]	£29,730
Efficacy: ≤ 300 pg/mL simple ITC	[redacted]	[redacted]	£25,373
Non-adherence adjustment: IPE method	[redacted]	[redacted]	£25,111

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
Persistence: 28% at 1 year (Reams et al)	[redacted]	[redacted]	£25,144
Utility gain (0.02) cinacalcet only	[redacted]	[redacted]	£27,251

Table 8 ERG additional analyses: ICERs for Etelcalcetide vs. cinacalcet

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
Company base case	[redacted]	[redacted]	£14,777
Efficacy: simple ITC etelecalcetide trials	[redacted]	[redacted]	£23,701
Efficacy: ≤ 300 pg/mL simple ITC	[redacted]	[redacted]	£11,490
Non-adherence adjustment: IPE method	[redacted]	[redacted]	£14,292
Persistence: 28% at 1 year (Reams et al)	[redacted]	[redacted]	£13,707
Utility gain (0.02) cinacalcet only	[redacted]	[redacted]	£42,761

The results of the ERG preferred analysis using the updated list price and PAS are summarised in Table 9. The assumptions underlying this analysis are summarised in section 4.4.3.1 of the ERG report (page 136). It combined two main changes to the company base case:

- use of a simple indirect treatment comparison to pool the results of the etelcalcetide trials (rather than the 'naïve' pooling used in the company base case), and
- use of the Iterative Parameter Estimation (IPE) method to adjust EVOLVE data for non-adherence (rather than the lag-censored analysis used in the company base case).

Table 9 ERG preferred analysis

	Incremental Costs	**Incremental QALYs**	**ICER (£/QALY)**
Etelcalcetide (with PB/VD) versus PB/VD alone			
Anticipated list price in CS ([redacted] per mg)	[redacted]	0.325	[redacted]
Confirmed NHS list price ([redacted] per mg)	[redacted]	0.325	[redacted]
Proposed PAS price ([redacted] per mg)	£8,879	0.325	£27,290
Etelcalcetide (with PB/VD) versus cinacalcet (with PB/VD)			
Anticipated list price in CS ([redacted] per mg)	[redacted]	0.044	[redacted]
Confirmed NHS list price ([redacted] per mg)	[redacted]	0.044	[redacted]

Proposed PAS price ([redacted] per mg)	£975	0.044	£22,400

The above analysis assumes that 8.9% of patients would achieve a reduction of >30% in PTH over 6 months without calcimimetic treatment (as in the pooled placebo arms of trials 20120229 and 20120230). However, as argued in section 4.4.3.2 of the ERG report, we consider that it is unlikely that this proportion would be the same for patients who had not responded to PB/VD treatment alone (the 'refractory' sub-group for whom cinacalcet is a comparator), as for patients with non-refractory SHPT (for whom PB/VD alone would be appropriate). We therefore repeated our sub-group analysis, assuming that 17.1% and 4.9% of non-refractory and refractory patients, respectively, would achieve >30% PTH reduction without calcimimetic. The results are shown in Table 10, and suggest that the following the ERG preferred analysis, the ICER would be below £30,000 per QALY for both comparisons.

Table 10 ERG preferred analysis with 'refractory' and 'non-refractory' subgroups

	Incremental Costs	**Incremental QALYs**	**ICER (£/QALY)**
Non-refractory to PB/VD alone (17.1% PTH response): Etelcalcetide (with PB/VD) versus PB/VD alone			
Anticipated list price in CS ([redacted] per mg)	[redacted]	0.308	[redacted]
Confirmed NHS list price ([redacted] per mg)	[redacted]	0.308	[redacted]
Proposed PAS price ([redacted] per mg)	£8,818	0.308	£28,626
Refractory to PB/VD alone (4.9% PTH response): Etelcalcetide (with PB/VD) versus cinacalcet (with PB/VD)			
Anticipated list price in CS ([redacted] per mg)	[redacted]	0.065	[redacted]
Confirmed NHS list price ([redacted] per mg)	[redacted]	0.065	[redacted]
Proposed PAS price ([redacted] per mg)	£1,051	0.065	£16,224

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre (SHTAC) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 23 January 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

We welcome the opportunity to review and comment on the ERG report. In this document we have provided our feedback in the following structure:

- ***Section 1.1 and 1.2**: Issues pertaining to the ERG's interpretation of our evidence submission that lead to misleading and potentially factually inaccurate conclusions*
- ***Section 2**: Factual inaccuracies (eg. typographical or reporting mistakes).*

Section 1. Issues with ERG interpretation of evidence leading to misleading and potentially factually inaccurate conclusions

Section 1.1 Issues relating to the scope of the company submission

Issue 1 **Summary: p10**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The summary of the scope of the company submission states: *The Evidence Review Group (ERG) considers that the submission **may not** provide evidence about the relative efficacy of etelcalcetide and cinacalcet in the population with refractory SHPT (this is discussed further below), and in this respect, the CS **does not** fully meet the scope of this appraisal.* We acknowledge that the evidence provided in support of etelcalcetide vs. cinacalcet in patients with refractory SHPT is derived from the phase 3 RCTs that did not specify refractory SHPT as an inclusion criterion. However, we consider that the evidence provided in our submission includes evidence for etelcalcetide vs. cinacalcet in patients with refractory SHPT based on the reasons outlined below. **1. Consistency of treatment effect across broad range of SHPT patients**	Proposed amendment: *The Evidence Review Group (ERG) considers that the submission may not provide evidence about the relative efficacy of etelcalcetide and cinacalcet in the population with refractory SHPT (this is discussed further below),~~ and in this respect, the CS does not fully meet the scope of this appraisal.~~* ***Evidence provided to support the relative efficacy of etelcalcetide and cinacalcet in the population with refractory SHPTs is subject to debate.***	To categorically state that the submission does not meet the scope is incorrect and may mislead the appraisal committee members to dismiss the evidence presented for a key subgroup of patients without due consideration.	The RCTs did not state refractory SHPT as an inclusion criterion, therefore it can only be inferred that some but not all? of the patients were refractory. It is not a factual error to state that the CS does not fully meet the scope of the appraisal. The use of the word 'fully' allows for the inference to be made that some patients may be considered to be refractory.

• Pre-specified subgroup analyses of the placebo-controlled trials (studies 20120229 and 230; combined n=1023) indicate the meaningful superior efficacy of etelcalcetide across the broad range of SHPT patients, including those with PTH levels >600 and >1000pg/mL, those using PB/VD at baseline and those with prior history of cinacalcet. • Pre-specified subgroup analyses of trial 20120360 are limited by the smaller sample size (n=683), which reduces the power to detect a statistically significant difference between etelcalcetide and cinacalcet in multiple sub-groups. Therefore confidence intervals around the point estimates of the odds ratios for the proportion of patients achieving >30% or >50% reduction from baseline in PTH levels for these subgroups are wide. However, the point estimates of the odds ratios are clearly and consistently in favour of etelcalcetide for patients with baseline PTH >900pg/mL, those using PB/VD at baseline and those with prior history of cinacalcet, and furthermore the relative effect size for etelcalcetide vs. cinacalcet for each of these subgroups is of similar magnitude to the effect size observed in the whole trial population. Indeed, the relative proportion of patients achieving a reduction in PTH concentrations of more than 30% did not differ significantly across any of the patient subgroups examined (see Figure 7			

of the EPAR and Figure 12 of our submission). Collectively, these data suggest that it is reasonable to infer that etelcalcetide is consistently efficacious across the broad population of patients enrolled in the trials, and therefore to adopt the relative effect size observed in the whole trial population. **2. Reflective of patients with SHPT refractory to PB/VD** • SHPT refractory to PB/VD cannot necessarily be defined by absolute PTH values alone as it may be appropriate to consider a change in PTH over time to determine whether a patient is/is not refractory to PB/VD. International clinical guidelines (KDIGO) recommend a PTH treatment target range of 2–9*ULN with marked changes in either direction within this ranged prompting an initiation or change in therapy to avoid progression to levels outside of this range. • However, we note that the ERG report states on page 38 that: "*Clinical expert advice to the ERG is that the baseline characteristics of participants in the trials are generally representative of patients seen in practice. The expert regarded the participants in the cinacalcet-controlled trial to have a higher median PTH (900*			

and 930 pg/mL in the etelcalcetide and cinacalcet trial arms respectively) than the median seen in clinical practice, ***but suggested this median PTH was reflective of the population who would currently be receiving cinacalcet****"*. • The ERG report also notes on page 23 that the clinical expert agreed that cinacalcet tends to be used to treat patients who are refractory to treatment with PB/VD, which would lend support to our contention that the etelcalcetide trial data provide evidence that is reasonably reflective of use in patients with refractory SHPT. We therefore consider that the evidence provided in our submission includes evidence for etelcalcetide vs. cinacalcet in patients with refractory SHPT. We acknowledge this requires interpretation and debate and understand this is the reason that the ERG has highlighted the evidence **may not** have been provided; however, we consider that on balance it is incorrect for the ERG to categorically state that the submission **does not** meet the scope.			

Issue 2 **Weaknesses and areas of uncertainty, p16**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *It is uncertain if, as the company argues, the subgroups of patient who had previously been treated with cinacalcet is representative of people refractory to treatment with PB/VD alone. The strength of this argument depends on how cinacalcet is used in the countries in which the trials took place – that is, whether it tends to be used as an initial treatment in a broad population of patients or as a second-line treatment for patients specifically with refractory SHPT. In this respect, the CS does not fully meet the company's decision problem or the final NICE scope.* Please see detailed response to Issue 1.	Proposed amendment: *It is uncertain if, as the company argues, the subgroups of patient who had previously been treated with cinacalcet is representative of people refractory to treatment with PB/VD alone. The strength of this argument depends on how cinacalcet is used in the countries in which the trials took place – that is, whether it tends to be used as an initial treatment in a broad population of patients or as a second-line treatment for patients specifically with refractory SHPT. ~~In this respect, the CS does not fully meet the company's decision problem or the final NICE scope.~~*	To categorically state that the submission does not meet the scope is incorrect and may mislead the appraisal committee members to dismiss the evidence presented for a key subgroup of patients without due consideration.	Please see our response to Issue 1.

Issue 3 **Summary of clinical effectiveness issues, p143**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…The key issue the ERG has identified*	Proposed amendment: *…The key issue the ERG has identified with the evidence presented*	To categorically state that the submission does not meet the scope is incorrect and may mislead	Textual amendments made as follows:

with the evidence presented in the CS is that there appears to be no data about the relative efficacy of etelcalcetide and cinacalcet among the patient population specified in the final scope and the company's decision problem to be of interest for this comparator; that is, people with refractory SHPT. The cinacalcet-controlled trial included a broad patient population and not those specifically with refractory SHPT. The company argues that subgroups of patients with a history of cinacalcet use in the three trials are likely to be representative of those with refractory SHPT. We suggest the strength of this argument depends on how cinacalcet is used in the countries where the trials were conducted (that is, whether it is used as an initial treatment in a broad range of patients or more specifically in those with refractory SHPT). In this respect, the CS does not fully meet the decision problem or the final scope. **Please see detailed response to Issue 1**	*in the CS is that ~~there~~ ~~appears to be no data~~* ***there is uncertainty in the extent to which the evidence provided by the company reflects the*** *relative efficacy of etelcalcetide and cinacalcet among ~~the patient population specified in the final scope and the company's decision problem to be of interest for this comparator; that is,~~ people with refractory SHPT,* ***a key population specified in the scope*** *The cinacalcet-controlled trial included a broad patient population and not those specifically with refractory SHPT. The company argues that subgroups of patients with a history of cinacalcet use in the three trials are likely to be representative of those with refractory SHPT. We suggest the strength of this argument depends on how cinacalcet is used in the countries where the trials were conducted (that is, whether it is used as an initial treatment in a broad range of patients or more specifically in those with refractory SHPT). ~~In this respect, the CS does not fully meet the decision problem or the final scope.~~*	the appraisal committee members to dismiss the evidence presented for a key subgroup of patients without due consideration.	"*The key issue the ERG has identified with the evidence presented in the CS is that ~~there~~ ~~appears to be no data~~* ***there is uncertainty in the extent to which the evidence provided by the company reflects the*** *relative efficacy of etelcalcetide and cinacalcet among ~~the patient population specified in the final scope and the company's decision problem to be of interest for this comparator; that is,~~ people with refractory SHPT,* ***a key population specified in the scope***. No amendment made to "*In this respect, the CS does not fully meet the decision problem or the final scope"* (please see our response to Issue 1)

Issue 4 Summary p41

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports:	Proposed amendment:	To categorically state that the submission does not meet the	See our response to Issue 1

... the ERG considers that the clinical effectiveness from the cinacalcet-controlled trial may not necessarily provide evidence about the relative efficacy of etelcalcetide versus cinacalcet among people with refractory SHPT (later in this report, in section 3.1.5, we consider it is uncertain if the subgroup analyses by previous cinacalcet use presented in the CS are representative of patients with refractory SHPT, as suggested by the company). In this respect, the CS does not fully address the decision problem and NICE's final scope…. **Please see detailed response to Issue 1.**	*... the ERG considers that the clinical effectiveness from the cinacalcet-controlled trial may not necessarily provide evidence about the relative efficacy of etelcalcetide versus cinacalcet among people with refractory SHPT (later in this report, in section 3.1.5, we consider it is uncertain if the subgroup analyses by previous cinacalcet use presented in the CS are representative of patients with refractory SHPT, as suggested by the company). ~~In this respect, the CS does not fully address the decision problem and NICE's final scope~~….*	scope is incorrect and may mislead the appraisal committee members to dismiss the evidence presented for a key subgroup of patients without due consideration.	

Issue 5 **Summary statement of company's approach, p52**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports: *…the CS does not provide evidence for the relative efficacy of etelcalcetide and cinacalcet among people with refractory SPHT, which was the population of interest*	Proposed amendment: *…the CS does not provide evidence for the relative efficacy of etelcalcetide and cinacalcet **derived specifically** among people with*	We provide evidence for this subgroup, but it is the ERGs interpretation that this may not reflect use in people with refractory SHPT.	Text amended as suggested.

in this appraisal for the cinacalcet comparator. **Please see detailed response to Issue 1**. As a point of consistency and accuracy, our submission details evidence that we feel, on balance, is highly likely to reflect the relative efficacy of etelcalcetide and cinacalcet in people with refractory SHPT.	*refractory SPHT, which was the population of interest in this appraisal for the cinacalcet comparator.*		

Issue 6 NICE Reference Case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1, Page 76 The ERG states that *"The population with refractory SHPT for whom cinacalcet is a comparator was not modelled"* **Please see detailed response to Issue 1.** As a point of consistency and accuracy, our submission details evidence that we feel, on balance, is highly likely to reflect the relative efficacy of etelcalcetide and cinacalcet in people with refractory SHPT.	*"~~The population with refractory SHPT for whom cinacalcet is a comparator was not modelled.~~There is uncertainty in the extent to which the evidence provided by the company reflects the population with refractory SHPT for whom cinacalcet is a comparator"*	To categorically state that the submission does not meet the scope is incorrect and may mislead the appraisal committee members to dismiss the evidence presented for a key subgroup of patients without due consideration.	We assume this Issue relates to Table 17, 4.3.1 page 79. This is not a factual error, no amendment made. See our response to Issue 1. In addition, we note that the economic model did not differentiate between background event risks in patients with refractory SHPT and in the 'broad licensed population' – thus the subgroup with refractory SHPT were not modelled. This point is explained further in sections 4.3.2.1 (page 82) and 4.3.2.3 (page 83-84) of our report.

Section 1.2 Other Issues

Issue 7 Summary of submitted clinical effectiveness evidence; p11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Report: *One phase III single arm study of the efficacy and safety of patients switching from cinacalcet to etelcalcetide (study 20120359, N = 158). The reasons for switching were not provided.* As noted in our submission, the purpose of the 359 study was to assess the safety and efficacy of switching patients from **stable cinacalcet** to etelcalcetide. The only reason for switching was participation in the study to assess whether or not patients could be safely switched to etelcalcetide from stable cinacalcet. There are therefore no reasons to report for switching.	Proposed amendment: *One phase III single arm study of the efficacy and safety of patients switching from cinacalcet to etelcalcetide (study 20120359, N = 158). ~~The reasons for switching were not provided.~~*	By stating that the reasons for switching are not provided suggests we have erroneously omitted to provide this detail, when in fact there are no details to provide.	Text amended as suggested.

Issue 8 **Summary of submitted clinical effectiveness evidence; p11**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…HRQoL in the cinacalcet-controlled trial did not appear to change substantially over time in either the etelcalcetide or cinacalcet arms, though scores were slightly lower in the etelcalcetide arm by week 26 (lower scores indicating reduced HRQoL).* This statement is over simplistic and has potential to mislead. The KDQOL-36 is a multicomponent HRQoL tool that does not have an overall summary score. There were very small numerical differences between the individual component scores for cinacalcet and etelcalcetide at all time points, including at baseline, and there is nothing to qualify the differences in terms of clinically meaningful / important differences. The only conclusion that can be drawn is that there did not appear to be substantial changes in HRQoL over time with either etelcalcetide or cinacalcet. The double-blind, double-dummy design of the 20120360 trial precluded assessment of the impact on HRQoL of reduced pill burden and greater patient convenience with etelcalcetide vs. cinacalcet. The unqualified	Proposed amendment: *…HRQoL in the cinacalcet-controlled trial* ***was similar for etelcalcetide and cinacalcet*** *~~in the active-controlled trial~~ and did not appear to change substantially over time in either arm.* ***The double-blind, double-dummy design of the cinacalcet-controlled trial would have precluded assessment of any potential impact on HRQoL arising from differences in administration and dosing with etelcalcetide vs. cinacalcet.*** *~~though scores were slightly lower in the etelcalcetide arm by week 26 (lower scores indicating reduced HRQoL)~~.*	The statement in the ERG report is over simplistic and inaccurate based on the available data, and has potential to mislead.	It is not factually incorrect to state that there were slightly lower scores at week 26 for etelcalcetide, and we did not state that the differences were clinically meaningful or important. The data are in the accompanying Table allowing readers to draw their own conclusion.

statement that "...*though scores were slightly lower in the etelcalcetide arm by week 26 (indicating reduced HRQoL)*" is therefore not warranted and has the potential to mislead. See also response to Issue 32.			

Issue 9 **Summary of submitted clinical effectiveness evidence, p12**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports: *….Rates of symptomatic hypocalcaemia events and cardiac failure were also higher with etelcalcetide than placebo or cinacalcet.*	Proposed amendment: *….Rates of symptomatic hypocalcaemia events and cardiac failure were also* ***numerically*** *higher with etelcalcetide than placebo or cinacalcet;* ***the rates of cardiac failure were consistent with background rates observed in placebo patients in the EVOLVE trial of cinacalcet.***	Numerical differences exist in CHF numbers but the EPAR notes confounding factors and number of events is limited, which does not allow firm conclusions to be drawn. Rates of CHF are consistent with background rate observed in placebo recipients in the EVOLVE trial. CHF included in risk management plan as a precaution.	Noted. Not a factual error.

Issue 10 **Weaknesses and areas of uncertainty, p15**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *The ERG's quality assessment of the included trials differed slightly to the company's assessment. We*	Proposed amendment: *… The ERG's quality assessment of the included trials differed slightly to the*	We consider that blinding was well preserved – the EPAR notes blinding was appropriate.	Text amended.

judged the three trials to be of a generally good quality, but considered it unclear if double-blinding had been adequately preserved and noted results for some outcomes were not ITT analyses, putting these at risk of attrition bias. Regarding whether blind had been preserved, see the detailed response to Issue 21. Regarding analyses not being conducted on an ITT basis and potential for attrition bias, see detailed response to Issue 22.	*company's assessment. We judged the three trials to be of a generally good quality, but considered it ~~unclear if~~ was **uncertain if double**-blinding had been ~~adequately~~ **completely** preserved. ~~and noted results for some outcomes were not ITT analyses, putting these at risk of attrition bias.~~*	The statement that some outcomes were not based on ITT analyses and so are at risk of attrition bias is incorrect.	

Issue 11 Weaknesses and areas of uncertainty, p16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *….drug doses in all three trials were titrated to a PTH target of <300pg/mL (31.8 pmol/L), but we suggest, based on clinical advice we received, that this is not reflective of clinical practice. The clinical expert consulted by the ERG noted 300pg/mL is in the middle of the 2-9 times the upper limit of normal reference range, but that in practice, clinicians would not specifically target this. That is, they would aim for a PTH range of 150 – 300 pg/ml (15.9 – 31.8 pmol/litre), but they would accept a PTH in the range of 2-9 times the upper limit of the normal reference range in selected patients (around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L) depending on levels of other parameters*	Proposed amendment: *….drug doses in all three trials were titrated to a PTH target of ≤300pg/mL (31.8 pmol/L). ~~, but we suggest, based on clinical advice we received, that this is not reflective of clinical practice.~~ The clinical expert consulted by the ERG noted 300pg/mL is in the middle of the 2-9 times the upper limit of normal reference range, but that in practice, clinicians would not specifically target this. That is, they would aim for a PTH range of 150 – 300 pg/ml (15.9 – 31.8 pmol/litre), but they would accept a PTH in the range*	We consider that the ERG statement overstates the extent to which the trial protocol deviates from clinical practice. The suggestion that the trials did not include a lower PTH range cut off is inaccurate.	We have amended the text to remove the comment about the lower range cut off. We have also amended the text to say "not necessarily reflective of clinical practice"

such as calcium and phosphate. Furthermore, the target used in the trials did not include a lower range cut-off, which means some participants may have been at risk of having their PTH over suppressed. Therefore, the treatment protocols (i.e. PTH target and drug doses administered to reach this target) used in the trials are not fully reflective of current practice in the UK. The clinical expert comments included in the ERG report highlight that in UK practice clinicians would aim for a PTH level in the range 150-300pg/mL, but they would accept a PTH in the range of 2-9 times the upper limit of the normal reference range in selected patients (around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L) depending on levels of other parameters such as calcium and phosphate. We note that the KDIGO clinical guidelines, on which the 2-9 x ULN range is based, states that: "*marked changes in PTH levels in either direction within this range prompt an* ***initiation or change*** *in therapy to avoid progression to levels outside of this range"*, and further states: " *In patients with CKD stage 5D and* ***elevated or rising*** *PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH"*. Etelcalcetide dose in the trials was titrated to PTH ≤300 pg/mL (which as noted by the ERG's clinical expert 300 pg/mL is within this range) but also required maintenance of adequate P and cCa levels. Dose suspension and subsequent dose reduction rules for low PTH (<100 pg/mL on 2 consecutive measurements), low serum (albumin corrected) calcium (<7.5 mg/dL), or symptomatic	*of 2-9 times the upper limit of the normal reference range in selected patients (around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L) depending on levels of other parameters such as calcium and phosphate.* ~~*Furthermore, the target used in the trials did not include a lower range cut-off, which means some participants may have been at risk of having their PTH over suppressed. Therefore, the treatment protocols (i.e. PTH target and drug doses administered to reach this target) used in the trials are not fully reflective of current practice in the UK.*~~		

hypocalcaemia were pre-specified and managed by interactive voice response systems based on PTH (blinded) and cCa levels determined the week before. Investigators remained blinded to conditions that required etelcalcetide dose suspension, as the interactive voice/web response system (IXRS) algorithm randomly selected a matched patient receiving placebo in whom to suspend dosing, and in the active-controlled trial, which employed a double-dummy design, the IXRS adjusted (i.e. increased /decreased/ suspended, as required) the placebo investigational product dose for both the IV and oral investigational products in the same subject. In summary, we consider that whilst a PTH target of 2-9 ULN was not specified, the targeting of PTH level in the middle of this range, whilst maintaining cCa levels, is reasonably reflective of the approach to drug dosing in clinical practice. The drug suspension and subsequent dose reduction required when PTH levels reached <100 pg/mL in effect provides a hard lower range cut off, in contrast to the assertion of the ERG that no lower cut-off was employed, and was implemented to help reduce the risk of PTH over suppression.			

Issue 12 **Weaknesses and areas of uncertainty, p17**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports:	Proposed amendment:	The statement in the EPAR implies	Not really a factual error but we

…The CS states the safety profile of etelcalcetide is similar to cinacalcet, but we consider this is not entirely justified: there were higher rates of asymptomatic decreased blood calcium (acknowledged in the company's interpretation of the evidence on CS p. 78), symptomatic hypocalcaemia and cardiac failure with etelcalcetide than cinacalcet. The incidence of symptomatic hypocalcaemia and cardiac failure were also clearly detailed in our submission on page 75-76 and in table 26, and symptomatic hypocalcaemia was also specifically mentioned on page 78 alongside asymptomatic hypocalcaemia. The specific mention of asymptomatic hypocalcaemia being acknowledged in the submission (without mention of the detailing of other adverse events) is likely to create the impression that we have not acknowledged these other adverse events in our submission, which is incorrect.	*…The CS states the safety profile of etelcalcetide is similar to cinacalcet, but we consider this is not entirely justified: there were* ***numerically small but*** *higher rates of asymptomatic decreased blood calcium ~~(acknowledged in the company's interpretation of the evidence on CS p. 78)~~, symptomatic hypocalcaemia and cardiac failure with etelcalcetide than cinacalcet.*	that symptomatic hypocalcaemia and cardiac failure are not acknowledged in our submission. This is incorrect.	have removed the reference to "*(acknowledged in the company's interpretation of the evidence on CS p. 78)"*

Issue 13 Description of company search strategies, p31

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *….These searches identified a phase II study of etelcalcetide among 37 adults with SHPT on haemodialysis,10 which was not identified by the company's clinical trial data searches (it*	Proposed amendment: *….These searches identified a* ***small, short-term*** *phase II* ***dose titration*** *study of etelcalcetide*	Risk of misleading the appraisal committee into believing this study was completely omitted form the CS with the current wording of the ERG Report.	Not a factual error. However, we have amended the text accordingly (on page 31) and also on page 40 (where the study was mentioned again).

was not listed among the included studies nor the excluded studies in the CS Appendix) despite the study being published online in December 2015… Thank you for noting this. We will raise this issue with the vendor that conducted the SLR. We are pleased to confirm that the study was still identified in our own company searches of trial data and was included in our submission as one of a number of non-randomised studies listed in Table 20, page 70. The study was not further discussed as it was a small (n=37) non-randomised, dose titration study of only 12 weeks duration. For the avoidance of doubt we suggest that the ERG's wording is further clarified to note the study, while absent from the SLR bibliography database searches, was still proactively identified by the company and detailed appropriately.	*among 37 adults with SHPT on haemodialysis,10 which was not identified by the company's clinical trial data searches (it was not listed among the included studies nor the excluded studies in the CS Appendix) despite the study being published online in December 2015;* ***however, the study was identified by the company and included as a non-randomised study, in the CS.***		

Issue 14 **Assessment of trial quality, Table 6, p42**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *Although all three trials were double-blinded, individual investigators adjusted background therapy. The background therapy was the same in all trial arms, however, it is not clear whether the effects of etelcalcetide may have influenced the need for background therapy adjustment, and if so whether this would have compromised blinding.* Background therapy could include PB. VD and other therapies felt necessary by the investigator to provide supportive care. VD doses were required to remain unchanged throughout unless dose reduction was necessary for safety reasons due to elevated cCa. Phosphate binders doses could be adjusted by the investigator in response to local P monitoring. *It was furthermore unclear how blinding was maintained because the CS did not provide information about whether patients in the comparator arms in all three studies underwent similar procedures to measure PTH and cCa concentrations to those in the etelcalcetide arms, which informed dose titration. It was also unclear who made decisions to titrate the dose and if they were blind to treatment allocation. The company's response to a clarification question about this suggests adequate procedures for performing dose titration were in place to blind investigators and patients to treatment allocation in the placebo-controlled trials (dose titration was performed*	Proposed amendment: ~~*…clinical expert advice received by the ERG suggests that the comparator cinacalcet has a noticeable effect in a short space of time on PTH levels, making it unclear if this may have an effect on background therapy adjustments and therefore on blinding. It is therefore unclear if blinding was fully preserved.*~~	The CS included details of the rapid onset of effect of etelcalcetide. It is incorrect to suggest there is a noticeable effect in a short space of time on PTH levels with cinacalcet, without also noting that etelcalcetide also has a rapid onset of effect on PTH.	Not a factual error but we have removed the text as suggested.

by an interactive voice/web response system), but it remained unclear what procedures were used in the cinacalcet-controlled trial. As noted in our response to clarification questions, routine local PTH monitoring was suspended during the three studies and investigational product dose titration (increase/ decrease/ maintenance) and dose titration or dose suspension was managed and determined by an interactive voice/web response system (IXRS) based on serum iPTH and cCa results obtained during the prior week. For clarification, in the placebo-controlled trials, the IXRS also assigned dose titration and suspension to placebo patients to mimic patients in the etelcalcetide group. As the active controlled trial used a double-dummy design, the IXRS adjusted (i.e. increased /decreased/ suspended, as required) the placebo investigational product dose for both the IV and oral investigational products in the same subject. Adequate procedures were therefore also in place to blind treatment allocation in the active controlled trial. *…clinical expert advice received by the ERG suggests that the comparator cinacalcet has a noticeable effect in a short space of time on PTH levels, making it unclear if this may have an effect on background therapy adjustments and therefore on blinding. It is therefore unclear if blinding was fully preserved.* Etelcalcetide also has a rapid effect on PTH levels, as noted in Figure 9 on page 63 of our submission. Approximately 35% of subjects receiving etelcalcetide in the RCTs had > 30% reduction in PTH from baseline at week 4 (i.e., before the first dose titration).			

We do not consider the rapid action of either agent would have compromised the blinding. In summary, extensive efforts were made to ensure blinding was preserved whilst ensuring appropriate safety guardrails were in place. The CHMP did not consider the blinding of the trials to have compromised the internal validity of the trials and the trial results, as reflected in the EPAR, which concludes (on page 56): "*The randomisation procedure is considered appropriate.* ***Blinding procedures are also considered appropriate****, as well as the applied visit schedules."* It is also relevant that the primary and secondary efficacy endpoints were objective endpoints based on laboratory parameters, rather than subjective endpoints. In addition specific safety events were adjudicated centrally in a blinded fashion. Combined with the dose titration and adjustment conducted via the IXRS, this would help to mitigate any residual risks of unblinding on key endpoint assessments.			

Issue 15 Description and critique of the approach to validity assessment, p43-44

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…The company's summary for the three etelcalcetide trials, however, does not point out issues around blinding, which are mentioned in the quality assessments in the CS appendix. If it was essential to*	Proposed amendment: *…The company's summary for the three etelcalcetide trials, however, does not point out issues around blinding, which are mentioned in the quality assessments in the CS appendix. If it*	As Issue 21 and Issue 22.	Text amended as suggested.

the management of the patient, centre personnel were un-blinded to the patient's individual treatment assignment (Table 6). As acknowledged in the CS appendix, it was also unclear if the central laboratory which carried out the biochemical assessments was blinded to the treatment assignment. We consider it was additionally unclear how blinding was maintained around dose titration in the cinacalcet-controlled trial. We also note that ITT analyses were used to analyse some outcomes and not others (further description of this is given in section 3.1.6 of this report). See detailed response to Issue 21 and Issue 22	*was essential to the management of the patient, centre personnel were un-blinded to the patient's individual treatment assignment (Table 6). As acknowledged in the CS appendix, it was also unclear if the central laboratory which carried out the biochemical assessments was blinded to the treatment assignment. ~~We consider it was additionally unclear how blinding was maintained around dose titration in the cinacalcet-controlled trial. We also note that ITT analyses were used to analyse some outcomes and not others (further description of this is given in section 3.1.6 of this report).~~*		

Issue 16 Summary of Health related quality of life, p61

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…In their response to the ERG's clarification question the company points out that the 26 week study duration is not long enough to reflect the clinical benefits associated with superior PTH control of etelcalcetide.* This is statement in the ERG does not fully convey the information we included in response to clarification questions on this subject. Our response stated:	Proposed amendment: *…In their response to the ERG's clarification question the company points out that the 26 week study duration is not long enough to reflect the clinical benefits associated with superior PTH control of etelcalcetide,* ***and the double-blind double-dummy design of the 20120360 trial precluded assessment of any***	Inadequate description of our response to clarification questions.	We acknowledge the point made about the double-blind double-dummy design, but there is no factual inaccuracy. In our judgement it was sufficiently informative just to mention the 26 week study duration as being insufficient to reflect changes in HRQoL.

"It should be noted that study 20120360 was of 26 weeks duration, which is sufficient to determine the superiority of etelcalcetide over cinacalcet for control of PTH levels, but is too short to capture improvements in clinical outcomes associated with this superior PTH control. The additional clinical benefit of etelcalcetide over cinacalcet would therefore not be captured in the KDQOL-36 results. In addition, study 20120360 had a double-dummy design, and so any impact of a lower pill burden and greater patient convenience of etelcalcetide versus cinacalcet (arising from its healthcare professional administration three times a week at the end of routine haemodialysis sessions, rather than daily oral therapy) is not reflected in the RCT and so would also not be captured in the results of KDQOL-36".	***impact on HRQoL of a lower pill burden and greater patient convenience of etelcalcetide versus cinacalcet.***		

Issue 17 The switch study (20120359), p67

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *In this study patients on a stable dose of cinacalcet switched to etelcalcetide after a seven day wash out period. It is not reported in the CS whether the patients were switched to etelcalcetide because of lack of*	Proposed amendment: *In this study patients on a stable dose of cinacalcet switched to etelcalcetide after a seven day wash out period. ~~It is not reported in the CS whether the patients were~~*	There are no reasons to report for switching beyond participation in the study. By stating reasons not provided implies we have erroneously omitted this detail, when in fact there are no reasons to detail.	Text amended accordingly

efficacy or adverse reactions or intolerability to cinacalcet. As noted in our submission, the purpose of the 20120359 study was to assess the safety and efficacy of switching patients from **stable cinacalcet** to etelcalcetide. The only reason for switching was participation in the study to assess whether or not patients could be safely switched to etelcalcetide from stable cinacalcet. There are therefore no reasons to report for switching.	*~~switched to etelcalcetide because of lack of efficacy or adverse reactions or intolerability to cinacalcet.~~*		

Issue 18 Summary of clinical effectiveness, p69

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…Participants who had previously received treatment with cinacalcet were more likely to respond to etelcalcetide than cinacalcet or placebo.* The same is true for those who had not previously received cinacalcet.	Proposed amendment: *…Participants ~~who had previously received treatment with cinacalcet~~ were more likely to respond to etelcalcetide than cinacalcet or placebo,* ***irrespective of prior history of cinacalcet use.***	Only highlighting etelcalcetide superiority in those with prior cinacalcet use is potentially misleading.	Text amended.

Issue 19 **Summary of clinical effectiveness, p69**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *HRQoL was measured in the cinacalcet-controlled trial only. HRQoL did not change substantially over time though scores were slightly lower in the etelcalcetide arm at week 26 (lower scores indicating reduced HRQoL).* This statement is over simplistic and has potential to mislead. The KDQOL-36 is a multicomponent HRQoL tool that does not have an overall summary score. There were very small numerical differences between the individual component scores for cinacalcet and etelcalcetide at all time points, including at baseline, and there is nothing to qualify the differences in terms of clinically meaningful / important differences. The only conclusion that can be drawn is that there did not appear to be substantial changes in HRQoL over time with either etelcalcetide or cinacalcet. The double-blind, double-dummy design of the 20120360 trial precluded assessment of the impact on HRQoL of reduced pill burden and greater patient convenience with etelcalcetide vs. cinacalcet. The unqualified statement that "...*though scores were slightly lower in the etelcalcetide arm by week 26 (indicating reduced HRQoL)*" is therefore not warranted	Proposed amendment: *HRQoL was measured in the cinacalcet-controlled trial only,* ***using the KDQOL-36. Small numerical differences in individual component scores were observed between treatment arms ate various time points, including at baseline, but*** *HRQoL did not change substantially over time* ~~*though scores were slightly lower in the etelcalcetide arm at week 26 (lower scores indicating reduced HRQoL).*~~ ***in either arm. The double-blind, double-dummy design would potentially limit the impact on HRQoL of any differences in administration and dosing between etelcalcetide and cinacalcet.***	Misleading to include an unqualified statement that implies lower HRQoL with etelcalcetide.	Please see our response to Issue 8

and has the potential to mislead. See also response to Issue 32.			

Issue 20 Summary of clinical effectiveness, p70

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: • *The patient population in the head-to-head trial of etelcalcetide versus cinacalcet consisted of a broad SHPT population, rather than the specific population of people with refractory SHPT (i.e. refractory to PB/VD alone) that was specified to be of interest in the final scope.* • *It is uncertain if the subgroups of participants in the trials who had previously been treated with cinacalcet are representative of people refractory to treatment with PB/VD alone, as the company suggests.* This summary ignores the comments on page 38 of the ERG report: *"Clinical expert advice to the ERG is that the baseline characteristics of participants in the trials are generally representative of patients seen in practice. The expert regarded the participants in the cinacalcet-controlled*	Proposed amendment: • *The patient population in the head-to-head trial of etelcalcetide versus cinacalcet consisted of a broad SHPT population, rather than the specific population of people with refractory SHPT (i.e. refractory to PB/VD alone) that was specified to be of interest in the final scope.* • *It is uncertain if the subgroups of participants in the trials who had previously been treated with cinacalcet are representative of people refractory to treatment with PB/VD alone, as the company suggests,* ***although the ERG clinical expert suggested the median PTH of patients in the trial was reflective of the population currently receiving cinacalcet in practice.***	More balanced summary of the evidence presented for this population.	Not a factual error.

trial to have a higher median PTH (900 and 930 pg/mL in the etelcalcetide and cinacalcet trial arms respectively) than the median seen in clinical practice, ***but suggested this median PTH was reflective of the population who would currently be receiving cinacalcet****"*			

Issue 21 Event Free Health State

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.2.1, Page 82 The ERG states that *"A second limitation of the CS modelled population is that all of the patients are assumed to enter the model in the 'event-free' state, without a previous CVD event or bone fracture (see section 4.3.3 below). However, the evidence base is not restricted to this group. As can be seen in Table 18, a proportion of patients in each of the four pivotal trials had a history of CVD and/or bone fracture at baseline. 12-14 , 38 These patients were at greater risk of subsequent CV or fracture event than patients without a history of CVD or fracture. In*	*"A second limitation of the CS modelled population is that all of the patients are assumed to enter the model in the 'event-free' state, without a previous CVD event or bone fracture (see section 4.3.3 below). However, the transition probabilities are directly calculated from EVOLVE, thus implicitly account for patients with prior events"* ~~*However, the evidence base is not restricted to this group.*~~ *As can be seen in Table 18, a proportion of patients in each of the four pivotal trials had a history of CVD and/or bone fracture at baseline. 12-14 , 38 These patients were at greater risk of subsequent CV or fracture event than patients without a history of CVD or fracture. In addition, a small proportion of the trial participants had undergone parathyroidectomy before randomisation."*	Misleading to not report on how quantification of transition probabilities impact this statement.	We agree that the transition probabilities will have incorporated event rates for patients with a previous event. However, as noted in section 4.3.2.2 (page 135) of our report, the QALY loss for a first event is higher than that for subsequent events. Thus modelling all patients as initially event-free will tend to overestimate the QALY gain from treatment. To clarify this point we have added the following text at the end of section 4.3.2.1 on page 82: *"The transition probabilities were calculated from*

addition, a small proportion of the trial participants had undergone parathyroidectomy before randomisation." The transition probabilities used in the model are calculated directly from the EVOLVE trial and thus implicitly account for patients with prior events – 46.8% history of CVD; 16.4% history of fracture). It is incorrect to simply state that the impact of prior events are not evaluated under the current model structure.			*EVOLVE and thus implicitly account for patients with prior events. However, the QALY loss associated with a first non-fatal CV event or fracture in the model is greater than that for subsequent events: the first event incurs a three-month utility loss for the acute period followed by an ongoing utility loss over the patient's lifetime, while a second event only incurs the acute period utility loss (see 4.4.2.2, page 135)."*

Issue 22 Non-adherence in etelcalcetide trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.1, Page 91 The ERG states that *"Non-adherence was also an issue in the etelcalcetide trials (CS Table 13, page 53), and the company presented two methods of adjusting for this: E) simple censoring of patients on discontinuation of the allocated*	~~*Non-adherence was also an issue in the etelcalcetide trials (CS Table 13, page 53), and the*~~ *The company presented two methods of adjusting for non-adherence in the etelcalcetide trials as the model structure required estimates of the on-treatment effect. These methods included: E) simple censoring of patients on discontinuation of the allocated study treatment; and F) the same ITT disaggregation method used for EVOLVE.*	It is potentially misleading to not report on why adjustments for non-adherence were conducted.	This is not a factual error, and we have not edited the text. We make the point about the model structure requiring adjustment for non-adherence in the first paragraph on page 88. This applies to the risk prediction method as for the EVOLVE based methods. Given this model structure, we consider that the imbalance in

study treatment; and F) the same ITT disaggregation method used for EVOLVE." Adjustments for non-adherence in the etelcalcetide trials were conducted to fit the model structure which required on-treatment estimates of efficacy. It is potentially misleading to not report why these analyses were necessary.			discontinuation from treatment in studies 20120229 and 20120230 did constitute an issue that needed to be addressed.

Issue 23 Lag censoring time

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.5, Page 100 ERG report states: "*The lag-censored approach yielded relatively conservative estimates compared with the other methods of adjusting for adherence. However, the choice of time lag is essentially arbitrary. Although the decision to use a six-month lag was based on discussions with clinicians, the 'correct' lag depends on various factors that are difficult*	*The lag-censored approach yielded relatively conservative estimates compared with the other methods of adjusting for adherence. ~~However, the choice of time lag is essentially arbitrary.~~ Although the decision to use a six-month lag was based on discussions with clinicians, the 'correct' lag depends on various factors that are difficult to assess: including the persistence of benefits of reduced calcification after cessation of treatment, and the timing of when patients in the placebo arm switched to cinacalcet or had parathyroidectomy*.	It is potentially misleading to conclude that the 6-month lag-time was 'essentially arbitrary' given the rationale provided – and acknowledged by the ERG – for this selection.	We disagree. As we note, the correct lag depends not just on anticipated duration of effects on skeletal calcification, but also on the cardiovascular effects of calcification, and the timing of when patients in the trial switched treatment. These factors are difficult to assess.

to assess: including the persistence of benefits of reduced calcification after cessation of treatment, and the timing of when patients in the placebo arm switched to cinacalcet or had parathyroidectomy." It is unfair to conclude that the choice of lag-time is 'essentially arbitrary' given that a lag time of 6-months was specified a priori as, in the view of clinical experts, it represented the anticipated duration that the effect of altered mineral metabolism had on extra skeletal calcification. This rationale is alluded to by the ERG in the subsequent sentence and contradicts the previous statement.			

Section 2 Issues relating to factual inaccuracies

Issue 24 Summary of submitted clinical effectiveness evidence; p10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *….. The trials included a total of 1023 participants (17 were from the UK).* Studies 20120229/230 included 10 patients from the UK	Proposed amendment: *….The trials included a total of 1023 participants (~~17~~ **10** were from the UK).* [Please note– the phase 3 RCTs have now been fully published and the number of patients from the UK are no longer AIC as available in supplementary content online]	Typographical error.	Amended

Issue 25 Summary of submitted clinical effectiveness evidence; p10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *One phase III, double-blind, multicentre RCT of etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) administered for 26 weeks in a broad population of people with CKD with SHPT, receiving haemodialysis (trial 20120360) (N = **515**; no patients from the UK).* Study 20120360 n=**683**	Proposed amendment: *One phase III, double-blind, multicentre RCT of etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) administered for 26 weeks in a broad population of people with CKD with SHPT, receiving haemodialysis (trial 20120360) (N = ~~515~~ **683**; no patients from the UK).*	Incorrect figure underestimates population size enrolled in key phase 3 trial.	Text amended

Issue 26 **Summary of submitted clinical effectiveness evidence; p11**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports: *The results of the trials showed participants treated with etelcalcetide (plus PB/VD) were statistically significantly more likely to achieve a > 30% reduction in mean PTH from baseline during EAP than those treated with placebo (plus PB/VD) (pooled analysis: 8.9% versus 75.3%, respectively, stratified odds ratio (95% confidence intervals (CIs)): 30.80 (18.18, 52.17), p < 0.001; data pooled from intention-to-treat (ITT) analyses).* These figures are incorrect – should be 8.9% vs. 74.7% OR 31.60 (21.59, 46.25), p <0.001	Proposed amendment: *The results of the trials showed participants treated with etelcalcetide (plus PB/VD) were statistically significantly more likely to achieve a > 30% reduction in mean PTH from baseline during EAP than those treated with placebo (plus PB/VD) (pooled analysis: 8.9% versus ~~75.3%,~~ **74.7%,** respectively, stratified odds ratio (95% confidence intervals (CIs)): ~~30.80 (18.18, 52.17)~~ **31.60 (21.59, 46.25**), p < 0.001; data pooled from intention-to-treat (ITT) analyses).*	Incorrect figures – possibly a transposition error.	Amended

Issue 27 **Current clinical practice, p23**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports: *The aim of treatment of SHPT among patients with CKD, receiving haemodialysis, is to manage phosphate, calcium and PTH levels so that they are within the normal ranges for dialysis patients. PB/VD are used to try to normalise calcium and phosphate levels. The CS does not outline how dietary modification to reduce phosphate levels is currently used in clinical practice. The clinical expert consulted by the ERG stated that in her clinic, patients are always referred to a dietician and dietary modification is always combined with treatment with PB/VD.* Section 3.2 our submission refers to dietary modification to reduce phosphate levels three times: in the context of NICE CG 157, NICE TA 117 and the KDIGO clinical guideline. We also confirmed in our response to clarification questions that dietary modification was included as usual background therapy in the the phase 3 RCTS of etelcalcetide. We therefore feel it is incorrect to state that the submission does not outline dietary modification to reduce phosphate levels.	Proposed amendment: *The aim of treatment of SHPT among patients with CKD, receiving haemodialysis, is to manage phosphate, calcium and PTH levels so that they are within the normal ranges for dialysis patients. PB/VD are used to try to normalise calcium and phosphate levels. ~~The CS does not outline how dietary modification to reduce phosphate levels is currently used in clinical practice. The clinical expert consulted by the ERG stated that in her clinic, patients are always referred to a dietician and dietary modification is always combined with treatment with PB/VD.~~* ***In addition to dietary modification, treatment may include medical management with phosphate binders, vitamin D analogues and calcimimetic, followed by parathyroidectomy in those patients with progressive disease who have exhausted medical therapies and are suitable for surgery.***	Factual inaccuracy.	We have made a minor amendment to remove the sentence “The CS does not outline how dietary modification to reduce phosphate levels is currently used in clinical practice”. We have added the following sentence: “Dietary modification can include reduction in phosphate intake”

Issue 28 **Potential impact of etelcalcetide on current service provision, p25**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *… Expert advice to the ERG is that administration would not add to the length of the dialysis session, unless it was administered as an infusion after dialysis but prior to rinse back (the expert noted it would not be administered after rinse back).* We feel the reporting of this comment from the ERG clinical expert is potentially open to misinterpretation and could be suggestive of unapproved administration of etelcalcetide. The SmPC clearly indicates that Parsabiv is administered by **bolus injection.** Furthermore, it states: *Parsabiv is administered into the venous line of the dialysis circuit at the end of the haemodialysis treatment* ***during rinse-back*** *or intravenously after rinse-back. When given during rinse-back at least 150 mL of rinse-back volume should be administered after injection.* ***If rinse-back is completed and Parsabiv was not administered, then it may be administered intravenously followed by at least 10 mL saline flush volume****.*	Proposed amendment: *… Expert advice to the ERG is that administration would not add to the length of the dialysis session~~, unless it was administered as an infusion after dialysis but prior to rinse back~~ (the expert noted it would not be administered after rinse back).*	To avoid any suggestion that etelcalcetide may/will be used outside of its SmPC-approved methods of administration.	Amended

Infusion of Parsabiv after dialysis but prior to rinse back, as stated by the ERG report, is not an approved mode of administration of Parsabiv. To avoid any misunderstanding, this should be removed.			

Issue 29 Summary, p25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports: *…In summary, the CS presents a generally accurate overview of current service provision, but does not clearly outline the PTH level used as a treatment initiation criterion nor discuss the role of dietary modification in treatment….* As discussed in Issue 12. We feel it is incorrect to state that our submission does not discuss the role of dietary modification. As noted in our submission, the prevalence of SHPT depends on the definition adopted.	Proposed amendment: *…In summary, the CS presents a generally accurate overview of current service provision, but does not clearly outline the PTH level used as a treatment initiation criterion ~~nor discuss the role of dietary modification in treatment….~~*	Factual inaccuracy.	Amended

Issue 30 **Patient population, p 26**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Reports: The patient population matches that specified in the final scope issued by NICE and that specified in the SmPC indication for etelcalcetide. Please note that the SmPC is now fully published. This, and any other information from the SmPC is now no longer AIC and highlighting can be removed.	Proposed amendment: *The patient population matches that specified in the final scope issued by NICE and that specified in the SmPC indication for etelcalcetide.* (i.e. removal of AIC highlighting from here and throughout doc where refers to SmPC)	SmPC information now fully published – not AIC	The AIC marking has now been removed

Issue 31 **Identified studies, p33**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *The SLR includes three, not yet fully published, phase III RCTs relevant to the decision problem:…* We can confirm that these studies are now fully published:	Proposed amendment: *The SLR includes three, ~~not yet fully published,~~ phase III RCTs relevant to the decision problem:*	Now fully published	Amended

Block GA, Bushinsky DA, Cunningham J, et al. Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Haemodialysis With Secondary Hyperparathyroidism Two Randomized Clinical Trials. *JAMA*. 2017;317(2):146-155 Block GA, Bushinsky DA, Cheng S, et al. Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism A Randomized Clinical Trial. *JAMA*. 2017;317(2):156-164			

Issue 32 **Identified studies, p34**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…We note, however, that doses were titrated to target PTH levels to <300 pg/mL (31.8 pmol/l) in all three trials…* As a point of accuracy, the dose was titrated to target PTH less than or equal to 300 pg/mL	Proposed amendment: *…We note, however, that doses were titrated to target PTH levels to ≤300 pg/mL (31.8 pmol/l) in all three trials…*	Point of accuracy.	Amended

Issue 33 Trial characteristics, Table 3, p35

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *Design:* Phase III, double-blind, placebo-controlled, multicentre RCT (111 renal centres in six countries; UK: n=17 CSR12) As a point of accuracy, there were 10 patients enrolled from UK in the 20120229 study. This information is no longer AIC as trials now fully published.	Proposed amendment: *Design:* Phase III, double-blind, placebo-controlled, multicentre RCT (111 renal centres in six countries; UK: ~~n=17~~ **n=10** CSR12) [Note: n=10 is not confidential]	Point of accuracy	Amended and AIC marking removed

Issue 34 Table 6, p43

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *Cinacalcet trial: ITT analyses were conducted of the 'achievement of a > 30% reduction in mean PTH from baseline during EAP' and 'achievement of mean PTH ≤ 300 pg/mL during EAP' outcomes, with missing data imputed appropriately using non-responder imputation. The number of participants stated in CS Tables 17 (p. 62) and 18 (p. 65) to be included in the analyses of the other trial outcomes suggest*	Proposed amendment: ~~*Comment: Placebo-controlled trials: ITT analyses were conducted of the secondary 'achievement of a > 30% reduction in mean PTH from baseline during EAP' endpoint and the outcomes 'achievement of a > 50% reduction in mean PTH from baseline during EAP' and*~~	All analyses were conducted on an ITT basis.	We have removed the text, in accordance with the company's explanation regarding the primary non inferiority outcome and multiple mutation. However, from the numbers of patients presented in CS Tables 17 and 18 it still appears that an ITT analysis was not used for some of the secondary

that these are not based on the ITT population, as smaller numbers are included than those randomised. And *Comment: Placebo-controlled trials: ITT analyses were conducted of the secondary 'achievement of a > 30% reduction in mean PTH from baseline during EAP' endpoint and the outcomes 'achievement of a > 50% reduction in mean PTH from baseline during EAP' and 'achievement of a mean pre-dialysis P ≤ 4.5 mg/dL during the EAP'. The number of participants stated in CS Tables 17 (p. 62) and 18 (p. 65) to be included in the analyses of the other trial outcomes suggest that these are not based on the ITT population, as smaller numbers are included than those randomised. See section 3.1.5 of this report for more information.* We acknowledge the potential for confusion with the figures that are presented in Tables 17 and 18 of our submission. However, the ERG report is incorrect – the Full analysis set (i.e. ITT) was used for the efficacy analyses, including the primary endpoint analysis and the secondary endpoint analyses in the three RCTs. The reason for the apparent discrepancy in the number of patients providing data is related to the methods used for imputing missing data. In the active-controlled trial the apparent discrepancy relates to the fact the primary non-	~~*'achievement of a mean pre-dialysis P ≤ 4.5 mg/dL during the EAP'. The number of participants stated in CS Tables 17 (p. 62) and 18 (p. 65) to be included in the analyses of the other trial outcomes suggest that these are not based on the ITT population, as smaller numbers are included than those randomised. See section 3.1.5 of this report for more information.*~~ ~~*Cinacalcet trial: ITT analyses were conducted of the 'achievement of a > 30% reduction in mean PTH from baseline during EAP' and 'achievement of mean PTH ≤ 300 pg/mL during EAP' outcomes, with missing data imputed appropriately using non-responder imputation. The number of participants stated in CS Tables 17 (p. 62) and 18 (p. 65) to be included in the analyses of the other trial outcomes suggest that these are not based on the ITT population, as smaller numbers are included than those randomised.*~~ *Comment: All efficacy analyses were conducted on an ITT-basis.*		analyses.

inferiority endpoint uses multiple imputation to impute missing data. The stratified treatment difference (with CI to demonstrate non inferiority) is based on all randomised patients using multiple imputation to impute missing data. It is not possible to present the proportions with this method of multiple imputation applied. Therefore, the proportions achieving the endpoint (63.9% vs 77.9%) are presented on the observed data (i.e. before imputation as noted in footnote a of Table 18), but the stratified treatment difference is analysed based on all randomised patients with multiple imputation for missing data (as noted in footnote b of Table 18). In contrast, the secondary superiority endpoints are analysed using non-responder imputation, for which it is possible to present the proportions including imputed missing data (footnote c of Table 18). All analyses in the placebo-controlled trial were also conducted on an ITT basis. In summary, the efficacy endpoints were all analysed on an ITT basis.			

Issue 35 Description and critique of company's outcome selection, p45

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *…the two placebo-controlled trials did use the more stringent PTH target of 'achievement of mean PTH ≤ 300*	Proposed amendment: *…the two placebo-controlled trials did use the more stringent PTH target of 'achievement of mean PTH ≤ 300 pg/mL*	It is inaccurate to state that no lower bound was employed for PTH when the IXRS implemented dose suspension and subsequent reduction in patients with PTH <100	Text amended

pg/mL during EAP' (note, though, that this does not have a lower bound limitation, which is important as very low PTH levels have been found to be associated with increased mortality, as does PTH levels that exceed the upper bound… As detailed in response to Issue 10, the IXRS controlled drug suspension and subsequent dose reduction implemented if PTH levels reached <100 pg/mL in effect provides a hard lower range cut off, in contrast to the assertion of the ERG that no lower cut-off was employed, and was implemented to help reduce the risk of PTH over suppression.	*during EAP' ~~(note, though, that this does not have a lower bound limitation, which is important as very low PTH levels have been found to be associated with increased mortality, as does PTH levels that exceed the upper bound…~~*	pg/mL.	

Issue 36 ITT analysis and other analysis sets, p48

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *For the cinacalcet-controlled trial 20120360, the CS presents the results for two different analyses of the outcome 'achievement of a > 30% reduction in mean PTH from baseline during EAP'. We note that the results presented as the primary, non-inferiority endpoint are not from an ITT analysis. The response rates presented are based on participant*	Proposed amendment: *~~For the cinacalcet-controlled trial 20120360, the CS presents the results for two different analyses of the outcome 'achievement of a > 30% reduction in mean PTH from baseline during EAP'. We note that the results presented as the primary, non-inferiority endpoint are not from an ITT analysis. The response rates~~*	Factual inaccuracy. Results of analyses are presented based on ITT using multiple imputation methods.	We note the explanation provided by the company, and have made some amendments to the text.

numbers before data imputation rather than the full randomised participant population. The CSR states the non-inferiority null method was used for data imputation in this analysis, but it is unclear what this method involves and no imputation appears to have been applied. In response to a clarification question about this (clarification response A5), the company stated this was a multiple imputation under the non-inferiority null method that used an assumed 60% response rate (based on the EVOLVE trial) for cinacalcet patients and a 48% response rate for etelcalcetide patients (based on the 12% non-inferiority margin) to impute response status. However, given that both the CS and CSR state the data presented for the primary endpoint are based on observed data without imputation, this imputation method does not appear to have been applied. Results are presented in both the CS and CSR without imputation. All analyses were conducted on the ITT population. As missing data for the primary non-inferiority analysis were imputed using multiple imputation it is not possible to provide imputed proportions for the endpoint – so the proportions presented in the submission are based on the observed data but the analyses are based on the ITT population with multiple imputation. See detailed response to Issue 22.	~~*presented are based on participant numbers before data imputation rather than the full randomised participant population. The CSR states the non-inferiority null method was used for data imputation in this analysis, but it is unclear what this method involves and no imputation appears to have been applied. In response to a clarification question about this (clarification response A5), the company stated this was a multiple imputation under the non-inferiority null method that used an assumed 60% response rate (based on the EVOLVE trial) for cinacalcet patients and a 48% response rate for etelcalcetide patients (based on the 12% non-inferiority margin) to impute response status. However, given that both the CS and CSR state the data presented for the primary endpoint are based on observed data without imputation, this imputation method does not appear to have been applied. Results are presented in both the CS and CSR without imputation.*~~		

Issue 37 **ITT analysis and other analysis sets, p49**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *The number of participants stated in CS Tables 17 (p. 62) and 18 (p. 65) to be included in the analyses of the other trial outcomes in all three trials suggest that these are not based on the ITT population, as smaller numbers are included than those randomised.* See response to Issue 22 and Issue 25.	Proposed amendment: ~~*The number of participants stated in CS Tables 17 (p. 62) and 18 (p. 65) to be included in the analyses of the other trial outcomes in all three trials suggest that these are not based on the ITT population, as smaller numbers are included than those randomised.*~~	Incorrect – all efficacy analyses based on ITT population.	Text removed. However, we still consider that it is uncertain if ITT analyses were used for all secondary outcomes (please see our response to issue 34).

Issue 38 **Summary of results for achievement of a > 30% reduction in mean PTH from baseline during EAP, p54-55**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *We note the etelcalcetide plus PB/VD and cinacalcet plus PB/VD response rates the company has selected for use in the economic model to extrapolate longer-term outcomes result in a 14.4% difference between the two*	Proposed amendment: *We note the etelcalcetide plus PB/VD and cinacalcet plus PB/VD response rates the company has selected for use in the economic model to extrapolate longer-term outcomes result in a 14.4% difference between the two treatments in the proportion of participants who*	Wording implies the primary analysis is not ITT. There is no need to qualify the 10.5% difference as based on ITT as all based on ITT.	Text amended

treatments in the proportion of participants who responded, favouring etelcalcetide. As stated, the company's approach to selecting these data breaks randomisation. We note that the cinacalcet-controlled trial (20120360), comparing cinacalcet plus PB/VD and etelcalcetide plus PB/VD, resulted in a 10.5% difference in the proportion of participants who responded, favouring etelcalcetide, when the ITT analysis was used. The primary no-inferiority analysis was also based on ITT analysis as detailed in Issue 22. Therefore the denominator in the analysis would be the same. – stating ITT is irrelevant	*responded, favouring etelcalcetide. As stated, the company's approach to selecting these data breaks randomisation. We note that the cinacalcet-controlled trial (20120360), comparing cinacalcet plus PB/VD and etelcalcetide plus PB/VD, resulted in a 10.5% difference in the proportion of participants who responded, favouring etelcalcetide, ~~when the ITT analysis was used.~~*		

Issue 39 **Summary of results for other measures of serum levels of PTH, p57**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographic errors: PB/VB stated twice on page 57. Should be PB/VD.		Typographic errors	Amended

Issue 40 **Summary of results for other measures of measures of serum calcium and phosphate levels, p59**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *None of these results were from ITT analyses.* All were ITT	Proposed amendment: ~~*None of these results were from ITT analyses.*~~	All efficacy analyses were ITT	Text amended, but see our response to Issue 34

Issue 41 **Summary of clinical effectiveness, p70**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: *Relatedly, drug doses in all three trials were titrated to a PTH target of <300pg/mL* As a point of accuracy, the dose was titrated to target PTH less than or equal to 300 pg/mL	Proposed amendment: *Relatedly, drug doses in all three trials were titrated to a PTH target of ≤300pg/mL*	Point of accuracy	Amended

Issue 42 The switch study (20120359), p67

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: • *Relatedly, drug doses in all three trials were titrated to a PTH target of <300pg/mL* As a point of accuracy, the dose was titrated to target PTH less than or equal to 300 pg/mL	Proposed amendment: • *Relatedly, drug doses in all three trials were titrated to a PTH target of ≤300pg/mL*	Point of accuracy	Amended

Issue 43 ERG meta-analysis of cinacalcet trials, p73

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We are unable to comment on the factual accuracy related to the ERG's exploratory meta-analyses, but note the significant heterogeneity in the analyses, and the ERG's and the comment on page 52 of the ERG report, which states: "*Statistically significant heterogeneity was present and this lends support to the justification not to conduct a*			Noted. No change necessary.

NMA."			

Issue 44 **Table 8, p56**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG reports: ERG Notes (2nd row): *Data from study 20120360 primary non-inferiority endpoint (not an ITT analysis; no imputation for missing data)* This is incorrect – as detailed in Issue 22, all efficacy analyses are ITT, including this analysis.	Proposed wording for ERG Notes (2nd row): *Data from study 20120360 primary non-inferiority endpoint ~~(not an ITT analysis; no imputation for missing data)~~*	Factual inaccuracy – is ITT based analysis	Text amended

Issue 45 **Terminology of comparisons in economic evaluation**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1, Page 76 The ERG states that "*The company developed an economic model to estimate the cost*	"*The company developed an economic model to estimate the cost effectiveness of etelcalcetide* ***in addition to standard therapy (PB/VD)*** *compared with cinacalcet* ***in addition to PB/VD****, or compared with* ***PB/VD*** ~~*standard therapy*~~ *alone* ~~*(PB/VD)*~~ *for treatment of SHPT in*	Amendment required to clarify comparisons used in the economic model, particularly as this is the first key introduction of the comparisons made.	Amended

effectiveness of etelcalcetide compared with cinacalcet, or compared with standard therapy alone (PB/VD) for treatment of SHPT in adult patients receiving haemodialysis for CKD"	*adult patients receiving haemodialysis for CKD*"		

Issue 46 Typographical error(s)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.2, Page 92 The ERG states that *"In unadjusted ITT analysis, there was no statistically significant improvement in the primary composite endpoint (0.93 HR, 95% CI 0.85 to 1.02)."* Section 4.3.4.2, Page 94 ERG report states: *"In EVOLVE, non-trial treatments that may have confounded results."* Section 4.3.4.2, Page 94 ERG report states: "As with RPSFTM, the company applied IPE used a full-recensoring	*In **the** unadjusted ITT analysis, there was no statistically significant improvement in the primary composite endpoint (0.93 HR, 95% CI 0.85 to 1.02)."* In EVOLVE, non-trial treatments ~~that~~ may have confounded results. *As with RPSFTM, the company applied IPE **which** used a full-recensoring method (to avoid informative censoring), and adjusted for diabetes, region and age.*	Typographical errors	Amended

method (to avoid informative censoring), and adjusted for diabetes, region and age.”			

Issue 47 **Etelcalcetide HRs from Log-Linear Extrapolation**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.3, Page 98, Table 22 The ERG report has copied a table from the company submission without accompanying footnotes which are necessary for interpretation.	Additional footnotes to Table 22 should be as follows: **[1]Myocardial infarction, unstable angina, heart failure and peripheral vascular event** **[2]Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials** **[3]Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin**	Point of accuracy	Amended

Issue 48 **Etelcalcetide HRs from Log-Linear Extrapolation**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.3, Page 98, Table 23 The ERG report has copied a table from the company submission without accompanying footnotes which are necessary for interpretation.	Additional footnotes to Table 23 should be as follows: **[1]Myocardial infarction, unstable angina, heart failure and peripheral vascular event** **[2]Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials** **[3]Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin**	Point of accuracy	Amended

Issue 49 **Etelcalcetide HRs based on Eandi et al.**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.4, Page 99, Table 24 Incorrect footnote label on Table	Footnote should read ‘1’ as opposed to ‘3’ in current ERG Report	Point of accuracy	Amended

23.			

Issue 50 Drug costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.5.5, Page 111 ERG report states: "*We checked the list prices and found minor inconsistencies in pricing for PB/VD. As these treatments are assumed to be identical across all treatment arms in the model, these minor discrepancies will have little effect on cost-effectiveness*." We have been unable to verify specifically where the minor inconsistencies in drug prices arise although acknowledge that these would be unlikely to impact the final results of the model.			We identified the cost of Sevelamer (0.8g 180 pack) as £74.11, rather than £96.58; and costs for alfacalcidol oral 1mcg, 0.25 mcg and 0.5 mcg 30 pack as £8.20, £2.92 and £6.34 respectively (rather than £4.65, £2.02, £4.39). These differences had a negligible impact on the model.

Issue 51 **Summary of cost-effectiveness**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.5, Page 141 ERG report states: "*We found the company's approach to costing, and measurement of HRQoL to be appropriate and consistent with the NICE Reference Case. Long-term costs of acute events were not included in the model, which is likely to result in an underestimation of costs. Utility estimates were"* Statement on utility estimates remains incomplete and should be rectified.		Point of accuracy	Thank you, we have added the following text: "*Utility estimates were obtained from a well-conducted analysis of EQ-5D data from the EVOLVE trial, which compared cinacalcet with placebo. In their base case analysis, the company did not include any direct utility effect associated with calcimimetic treatment (in addition to the utility benefits associated with prevention of CV events, fractures, and parathyroidectomy). They conducted a scenario analysis, assuming equal utility gains with etelcalcetide as had been observed with cinacalcet. However, it is uncertain whether this assumption is valid.*"