Etelcalcetide for treating of secondary hyperparathyroidism [ID908]

Cost effectiveness

1st Committee meeting

8th February 2017

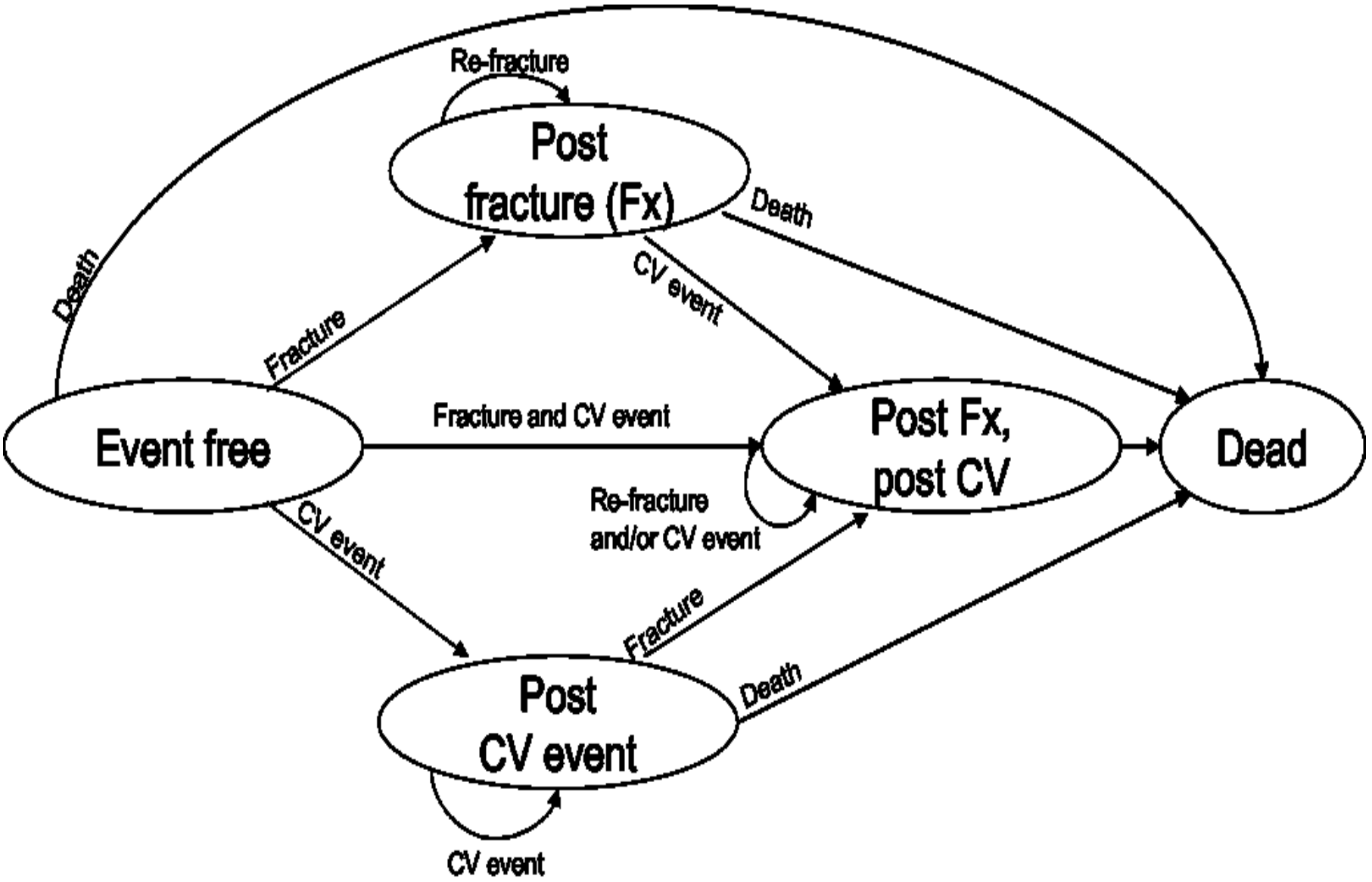
Committee A

Ellen Rule

Key issues - cost effectiveness

- Data from another trial (of cinacalcet) was used to predict the long term outcomes of survival and incidence of cardiovascular events. Is this reasonable?
- 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
- Company model excluded longer-term savings or health effects that might be associated with parathyroidectomy. Is this appropriate?
- Innovation: IV vs oral therapy

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)

R A N D O M I S E D 1 : 1

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)

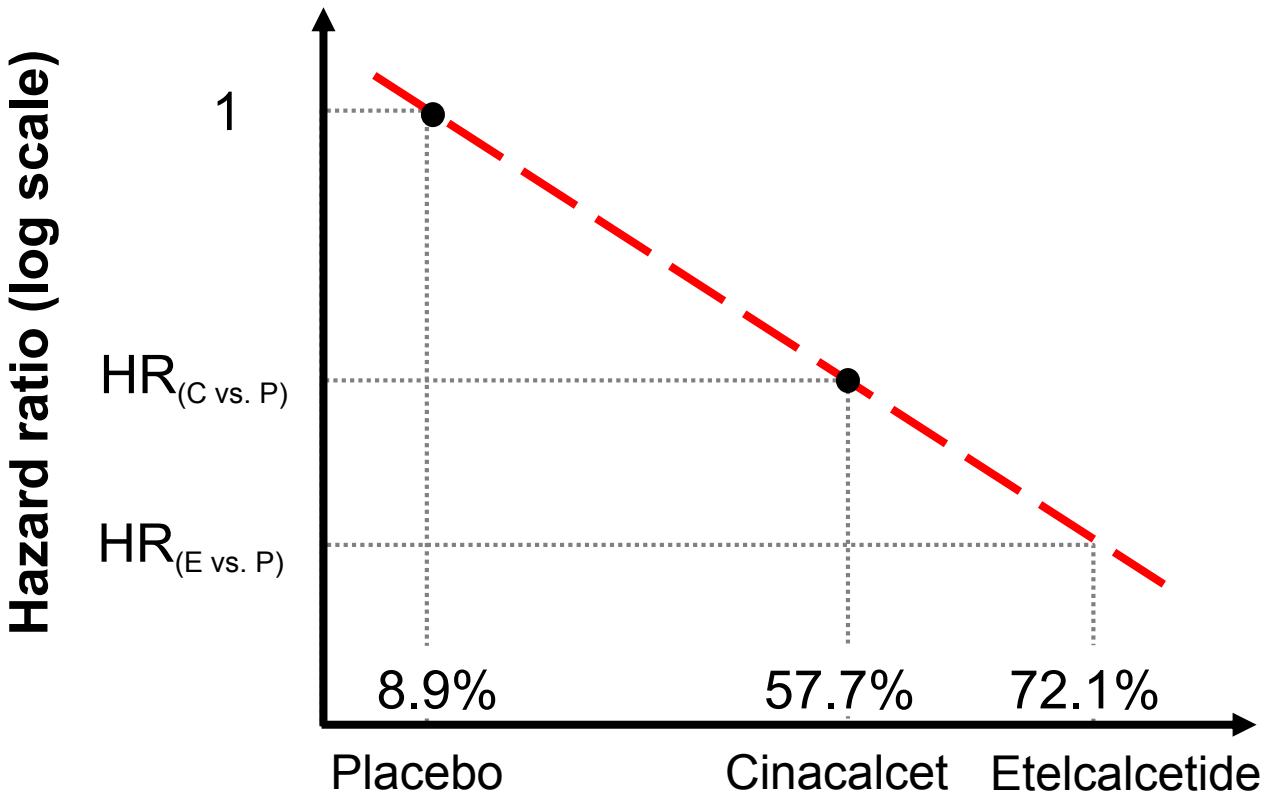
Secondary outcomes:
- Time to individual components of composite endpoint
- Time to stroke, bone fracture & PTx
- Biochemical measurements (% achieving >30% reduction in PTH not reported)

EVOLVE trial: results

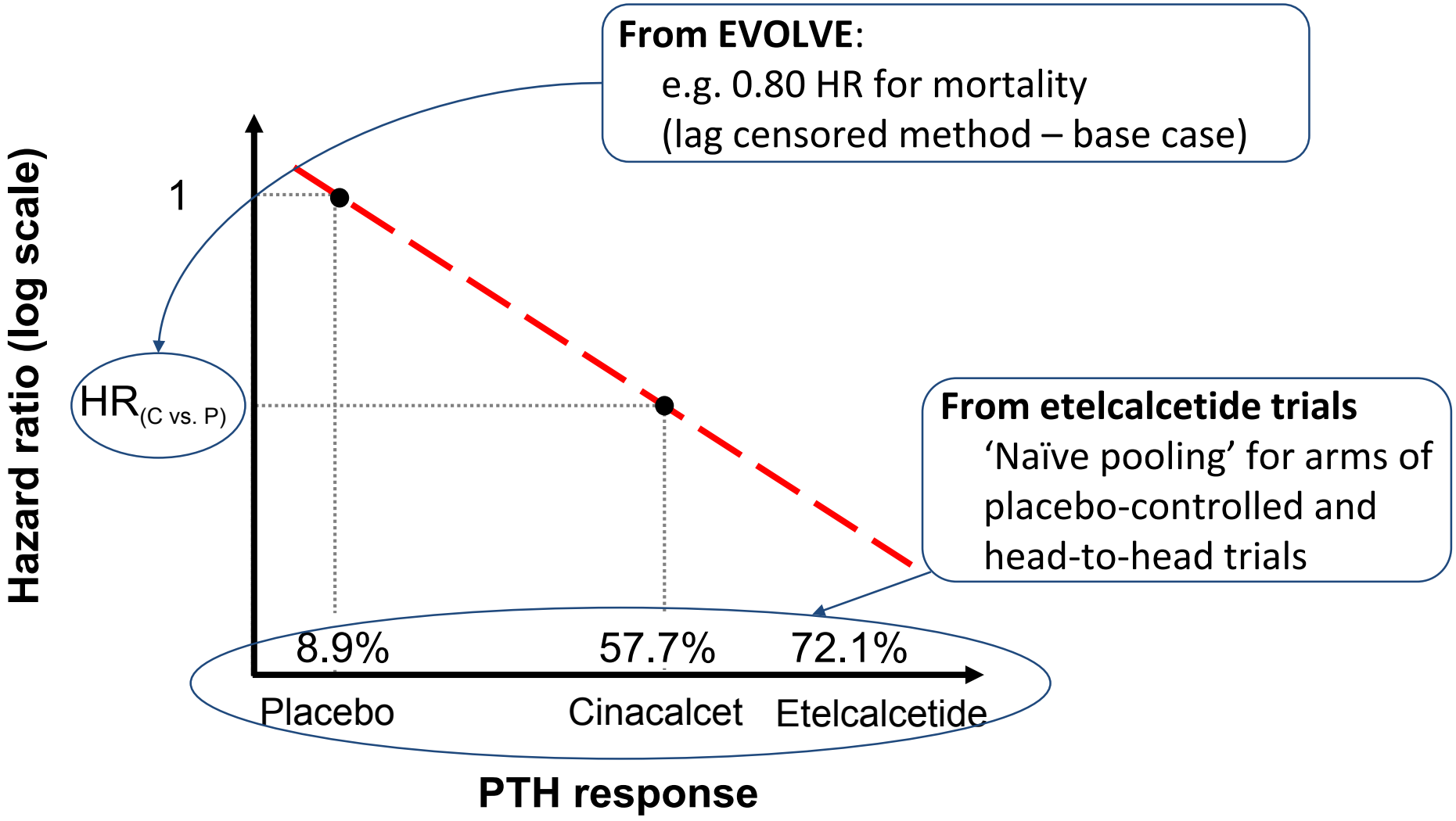
Method of analysis	All-cause mortality	Nonfatal CV event	Bone fracture	PTx
ITT	XXX XXXXXXX	XXX XXXXXXX	XXX XXXXXXX	XXX XXXXXXX
ITT adjusted *	0.87 [0.78, 0.97]	0.85 [0.74, 0.97]	0.86 [0.72, 1.04]	0.42 [0.34, 0.51]
Lag-censored (base case) *	**0.80 [0.69, 0.91]**	**0.78 [0.67, 0.91]**	**0.73 [0.59, 0.92]**	**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 *	XXX XXXXXXX	XXX XXXXXXX	XXX XXXXXXX	XXX XXXXXXX
IPE *	XXX XXXXXXX	XXX XXXXXXX	XXX XXXXXXX	XXX XXXXXXX

* Adjusted for baseline covariates

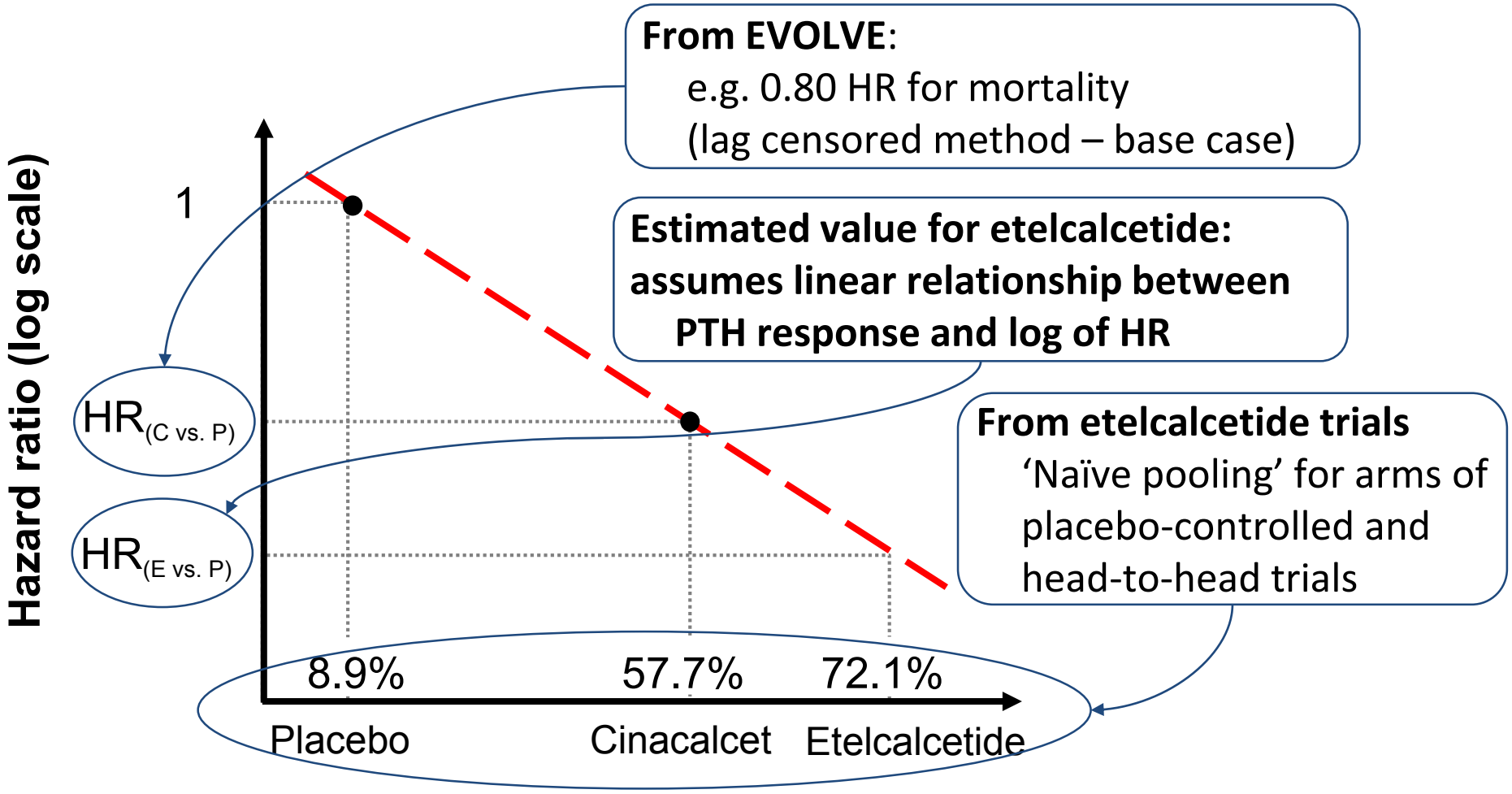
Extrapolation of EVOLVE HRs to etelcalcetide



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	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

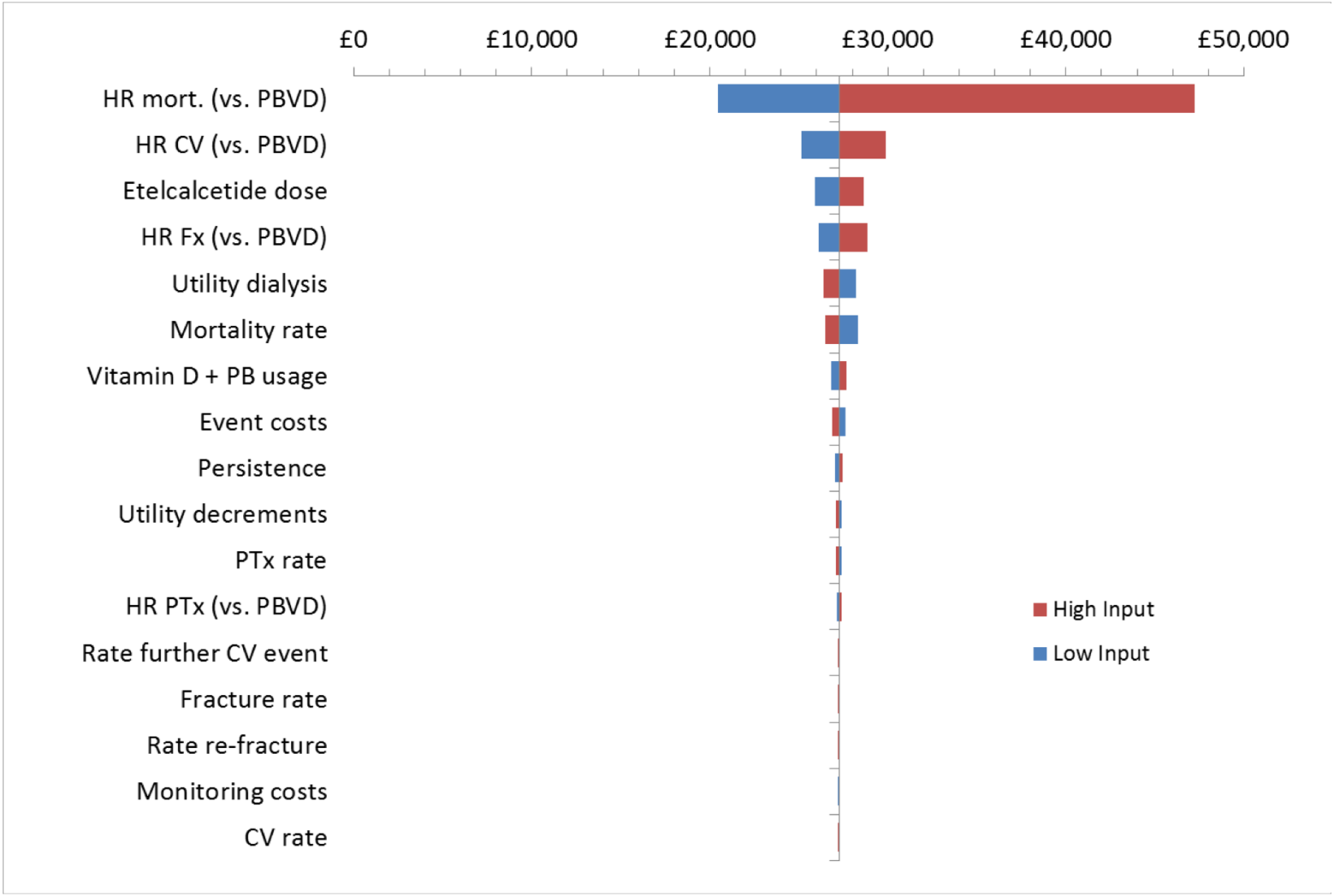
Reference case – ERG comments

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

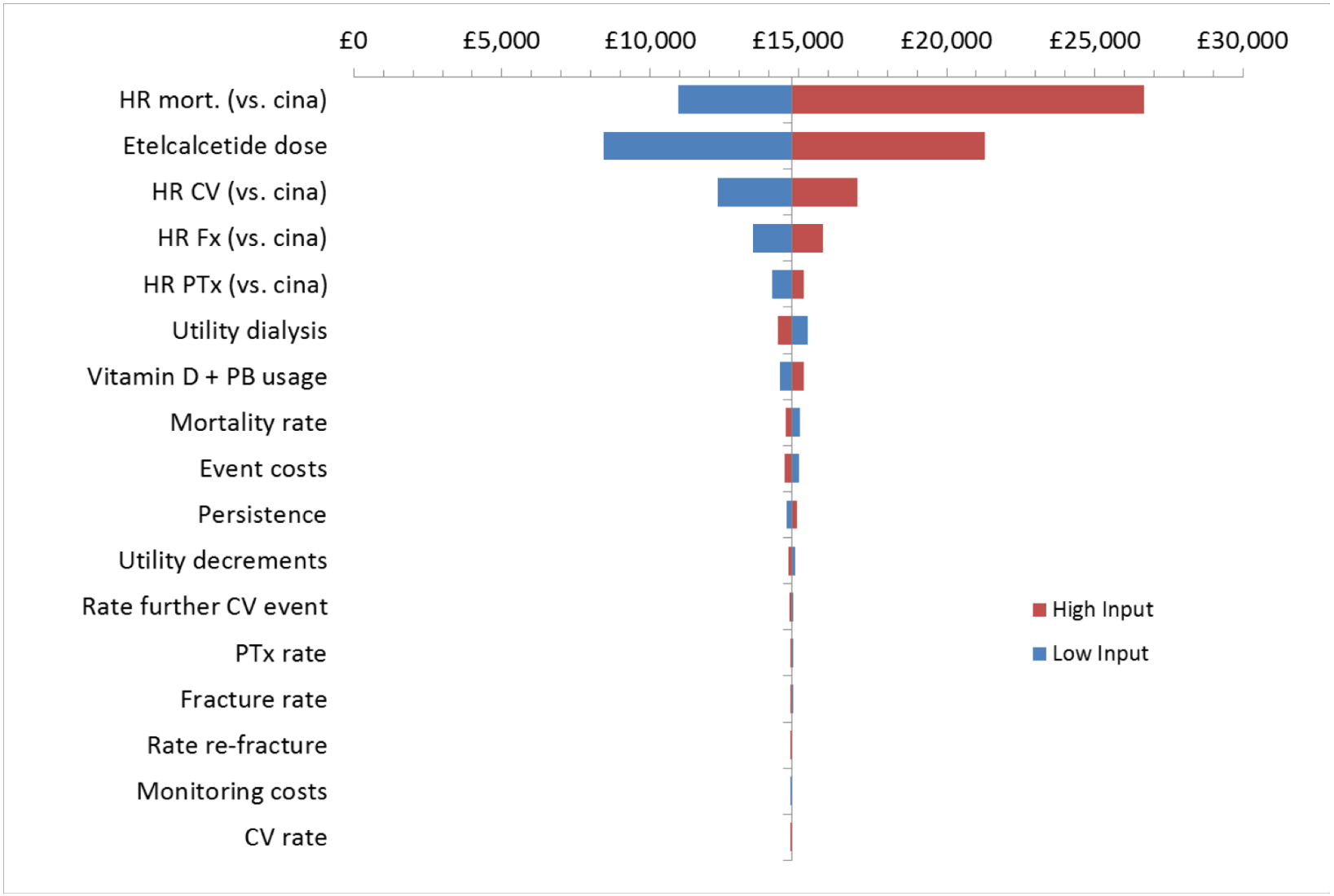
Cost effectiveness results – company base case

	Total Costs	Incremental Costs	Total QALYs	Incr. QALYs	ICER (£/QALY)
Broad licensed population (etelcalcetide vs. PB/VD)					
PB/VD	XXXXXX	-	3.788	-	-
Etelcalcetide*	XXXXXX	£8,738	4.109	0.321	£27,251
Population with refractory SHPT (etelcalcetide vs. cinacalcet)					
Cinacalcet*	XXXXXX	-	4.040	-	-
Etelcalcetide*	XXXXXX	£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

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

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 etelcalcetide 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
4. 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	Incr. Costs	Incr. QALYs	ICER £/QALY
Non-refractory to PB/VD alone (8.9% target PTH reduction)					
PB/VD alone	XXXXXX	3.788			
Etelcalcetide *	XXXXXX	4.114	£8,879	0.325	£27,290
Refractory to PB/VD alone (8.9% target PTH reduction)					
Cinacalcet *	XXXXXX	4.070			
Etelcalcetide *	XXXXXX	4.114	£975	0.044	£22,400

QALYs, quality-adjusted life-years; Incr, incremental; 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 - cost effectiveness

- Data from another trial (of cinacalcet) was used to predict the long term outcomes of survival and incidence of cardiovascular events. Is this reasonable?
- 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
- Company model excluded longer-term savings or health effects that might be associated with parathyroidectomy. Is this appropriate?
- Innovation: IV vs oral therapy