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Economic Evaluation of Cinacalcet in the United States: The EVOLVE Trial

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ABSTRACT

Background: Previous economic evaluations of cinacalcet in patients with secondary hyperparathyroidism (sHPT) relied on the combination of surrogate end points in clinical trials and epidemiologic studies. **Objectives:** The objective was to conduct an economic evaluation of cinacalcet on the basis of the EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial from a US payer perspective. **Methods:** We developed a semi-Markov model to assess the cost-effectiveness of cinacalcet in addition to conventional therapy, compared with conventional therapy alone, in patients with moderate-to-severe sHPT receiving hemodialysis. We used treatment effect estimates from the unadjusted intent-to-treat (ITT) analysis and prespecified covariate-adjusted ITT analysis as our main analyses. We assessed model sensitivity to variations in individual inputs and overall decision uncertainty through probabilistic sensitivity analyses. **Results:** The incremental cost-effectiveness ratio (ICER) for cinacalcet was $61,705 per life-year and $79,562 per quality-adjusted life-year (QALY) gained using the covariate-adjusted ITT analysis. Probabilistic sensitivity analysis suggested a 73.2% chance of the ICER being below a willingness-to-pay threshold of $100,000. Treatment effects from unadjusted ITT analysis yielded an ICER of $115,876 per QALY. The model was most sensitive to the treatment effect on mortality. **Conclusions:** In the unadjusted ITT analysis, cinacalcet does not represent a cost- effective use of health care resources when applying a willingness-to-pay threshold of $100,000 per QALY. When using the covariate-adjusted ITT treatment effect, which represents the least biased estimate, however, cinacalcet is a cost-effective therapy for patients with moderate-to-severe sHPT on hemodialysis.

Keywords: cinacalcet, cost-effectiveness, dialysis, hyperparathyroidism.

Introduction

Patients suffering from end-stage renal disease (ESRD) frequently develop secondary hyperparathyroidism (sHPT), a progressive disease associated with persistent elevations in serum concentrations of biochemical markers of mineral metabolism including parathyroid hormone (PTH), calcium, and phosphate [1]. The goal of sHPT treatment is to manage the biochemical markers of mineral metabolism, which are linked to cardiovascular (CV) events and fractures by extensive epidemiologic evidence [2–5]. These complications are burdensome to patients and worsen the already heavy financial costs of dialysis [6–8]. Various forms of vitamin D sterols and phosphate binders along with dietary phosphorus restriction have traditionally been used in clinical practice to manage sHPT. For patients with more severe disease and who fail to respond adequately to medical therapy, total or partial surgical removal of parathyroid glands, that is, parathyroidectomy, is considered a viable option according to current practice guidelines [9].

Over the last decade, cinacalcet, a calcimimetic agent, has been added to conventional therapies for this indication because it effectively suppresses PTH [10]. Cost-effectiveness analyses of cinacalcet have been previously published in the United States [11,12], Europe [13–15], and Japan [16]. Boer et al. [11] reported that cinacalcet could be considered cost-effective in the United States if the willingness-to-pay threshold was $100,000 per quality-adjusted life-year (QALY), while Ray et al. [12] found that cinacalcet could be cost-effective if initiated in patients with less severe, compared to more severe, sHPT. The European analyses [13,14] also found acceptable cost-effectiveness results for cinacalcet in five European countries. In contrast, the study by Garside et al. [15] concluded that cinacalcet was unlikely to be

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cost-effective from the UK payer perspective. Last, the analysis considering Japanese settings [16] concluded that cinacalcet was likely to be cost-effective only for those patients who cannot undergo surgical parathyroidectomy. The seemingly inconsistent conclusions of these reports reflect heterogeneity of the modeling assumptions and costs across regions.

One important aspect that is common across previously published cost-effectiveness analyses is the reliance on trials using surrogate outcomes, that is, laboratory markers of sHPT such as PTH, calcium, and phosphate, to ascertain efficacy estimates. Then, lifetime projections for survival and costs are derived from risks attributable to these laboratory parameters based on large epidemiologic studies (e.g., as shown in Block et al. [4]). Although common in modeling studies, this approach relies on the assumption that surrogate markers do indeed affect hard outcomes. This important gap can be addressed only in a randomized trial designed to assess effects of a therapy on hard outcomes.

The EValuation Of Cinacalcet HCl Therapy to Lower Cardio-Vascular Events (EVOLVE) randomized controlled trial [17] examined the effects of cinacalcet on hard outcomes. Although the EVOLVE trial failed to show a statistically significant benefit of the active treatment group compared with placebo using an unadjusted intent-to-treat (ITT) analysis, an ITT analysis adjusted for baseline characteristics, lag-censoring, and other analyses showed nominally significant reductions in the risk of death or major CV events. Completion of the EVOLVE trial made it possible to address the important gaps in the economic evaluations of cinacalcet highlighted above, particularly by providing a robust data set in which the estimates of effects of cinacalcet on hard outcomes were directly evaluated within the scope of the trial. The objective of this article was to provide an economic evaluation of cinacalcet in the context of the US health care system using data from the EVOLVE trial.

Methods

Clinical Trial

EVOLVE was a global, double-blind, randomized, placebo-controlled trial evaluating the effects of cinacalcet versus placebo, both in addition to conventional therapy, that is, vitamin D sterols and phosphate binders, on death or major CV events in patients with moderate-to-severe sHPT receiving hemodialysis [17]. Major baseline covariates included demographic and clinical characteristics, comorbidities, and history of CV events and fractures (Table 1). The primary composite end point in the EVOLVE study was death or first nonfatal myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. Secondary end points included CV death, stroke, clinical fracture (there was no radiologic screening for fractures during the trial), and parathyroidectomy. Laboratory-based outcomes and health-related quality of life were also assessed. The primary unadjusted ITT analysis showed that patients randomized to cinacalcet experienced numerically fewer composite events, but the risk reduction was not statistically significant (relative hazard 0.93; 95% confidence interval [95% CI] 0.85–1.02; $P = 0.11$).

The analysis of baseline characteristics revealed that patients randomized to cinacalcet were approximately 1 year older than those randomized to placebo. The age imbalance was manifested at the extremes of the distribution, with fewer patients randomized to cinacalcet than to placebo in the younger than 50 years age group in which the risk of clinical events is lower. In addition, more patients randomized to cinacalcet than to placebo were in the older than 70 years age group in which the risk of clinical events is particularly high. It is likely that the observed age imbalance occurred by chance because the likelihood of imbalance is dictated by the SD for age and the sample size. The probability of an age difference of more than 0.8 years occurring in the EVOLVE trial was 0.08, as the SD for age was 14 years, which is larger than in other CV trials. In comparison, owing to more restrictive inclusion criteria and older patients enrolled, the SD for age was lower in the Study of Heart and Renal Protection (SHARP) trial [18]—12 years—and the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [19] trial—10 years, with a probability of observing an age difference of more than 0.8 years between groups of 0.04 and 0.01, respectively (P.S. Parfrey PS, G.A. Block, R. Correa-Rotter R, et al., unpublished data, 2015). The prespecified analysis adjusting for baseline characteristics including age showed a relative hazard of 0.88 (95% CI 0.79–0.97; $P = 0.008$) for the primary composite end point, or a nominally statistically significant 12% risk reduction with cinacalcet than with placebo.

Table 1 – Demographic and clinical characteristics by treatment group*.

Characteristic	Cinacalcet (N = 1948)	Placebo (N = 1935)
Age (y), median (10%–90%)	55.0 (35.0–74.0)	54.0 (35.0–73.0)
Sex: female (%)	41.5	39.7
Race or ethnic group (%)		
White	57.7	57.7
Black	21.0	22.1
Other	21.3	20.2
Body mass index (kg/m^2), median (10%–90%)	26.3 (20.4–36.4)	26.4 (20.6–36.7)
Months on dialysis, median (10%–90%)	45.4 (8.5–142.0)	45.1 (9.9–149.6)
Medical history (%)		
Diabetes	33.6	33.5
Cardiovascular disease, including hypertension	95.4	94.6
Heart failure	23.1	23.6
Peripheral vascular disease	16.1	16.6
Myocardial infarction	12.3	12.6
Stroke	8.3	10.0

* These baseline characteristics, along with region, tobacco use, type of vascular access, blood pressure, high-density lipoprotein, calcium-phosphate product (CAxP), and albumin, were included in the covariate-adjusted analysis. There were no significant differences between the two groups except for mean diastolic blood pressure ($P = 0.02$) and transient ischemic attack ($P < 0.05$).

The study drug discontinuation rates were high: 67% and 71% in the groups randomized to cinacalcet and placebo, respectively. Off-protocol (commercial) cinacalcet was commonly prescribed after study drug discontinuation—11.4% and 19.8% in the groups randomized to cinacalcet and placebo, respectively. This cross-over effect, that is, discontinuation of study drug in the cinacalcet group and use of commercial cinacalcet in the placebo group, is expected to reduce the observed effect size. To minimize this cross-over effect, a prespecified lag-censoring analysis was conducted. This lag-censoring analysis used the full ITT cohort but censored the follow-up time at 6 months postdiscontinuation [17] and was intended to take account of drug effects that may persist after discontinuation. The results showed a consistent treatment effect for cinacalcet, with a relative hazard risk of 0.85 for the primary composite end point (95% CI 0.76–0.95; $P = 0.003$), or a 15% nominally statistically significant reduction in risk. The

consistency of results was further supported by more extensive statistical methods fully described elsewhere [20]. The primary ITT analysis, as well as the prespecified covariate-adjusted and lag-censored analysis, is described in the EVOLVE primary manuscript [17].

We analyzed the cost-effectiveness of cinacalcet using a range of clinical effect estimates—unadjusted and covariate-adjusted ITT, and lag-censoring. Because controlling for baseline covariate imbalances will improve the internal validity of the estimate, the covariate-adjusted ITT analysis is the least biased and the most relevant for the payer perspective. The unadjusted ITT analysis is likely biased because of the age imbalance, and the lag-censoring analysis, while also interesting because it reflects the effects of the medication when patients actually take it and is less relevant for a "real-world" situation in which adherence is imperfect. Therefore, we focused primarily on the adjusted and unadjusted ITT analyses, and used lag-censoring treatment effects as a part of scenario analyses.

Model Overview

We developed a semi-Markov model to assess the cost-effectiveness of cinacalcet plus conventional therapy (referred to as the cinacalcet group) compared with conventional therapy (referred to as the conventional therapy group) in patients with sHPT receiving hemodialysis. Consistent with the EVOLVE trial inclusion criteria, the model population was defined as adults with ESRD who had been treated with maintenance hemodialysis three times a week for 3 months or more who had a PTH level of 300 pg/ml or more, serum calcium level of 8.4 mg/dl or more, and calcium-phosphorus products level of 45 mg^2/dL^2 or more. Conventional therapy was administered at the treating physician's discretion and typically, but not always, included vitamin D sterols and phosphate binders.

A patient cohort enters the model in the event-free health state (Fig. 1). The transitions from the event-free state are to the following states: Nonfatal CV event: In this health state, patients are alive and are experiencing myocardial infarction, hospitalized unstable angina, heart failure, or peripheral vascular event; and fracture: In this health state, patients are alive and are experiencing a clinical fracture.

The postevent states (modeled as a series of three short-term tunnel states and one long-term postevent state) defined over the course of 1 year after an event allow the model to account for any lingering effects on health-related quality of life and for the potential increased costs after the events. After the postevent state, the event rates and costs return to those associated with the event-free health state. Patients in the postevent states can transition back to CV events, parathyroidectomy, or remain in the postevent health states. Patients may transition to the death health state from any other health state in the model.

To be consistent with the design of the EVOLVE trial, parathyroidectomies were modeled as outcomes; that is, at the time of parathyroidectomy, the costs of surgery including follow-up costs and disutilities were applied, and patients continued to be at risk for other outcomes.

The lack of memory in the semi-Markov model could lead to an underestimation of the impact of subsequent events of different types on costs and utilities in our analysis. For example, a fracture after a CV event would have a greater effect on quality of life than one of the two outcomes alone. We addressed this through the use of state prevalence estimates of the expected number of patients in the postevent health states. Costs and QALYs were adjusted proportionality to the number of patients in the postevent states expected to have both outcomes (fracture and CV event) simultaneously. To avoid double counting, we did not apply the above calculations for transitions between events of the same type, and assumed the cost and disutilities of the acute event taking precedence over those of the chronic event.

The model assumed a lifetime horizon and used a 3-month cycle. We discounted all costs and outcomes at 3% per year. We developed the model using Microsoft Excel for Windows.

Model Inputs

Model inputs include clinical, economic, and health-related quality-of-life data; these were estimated from patient-level data analysis of the EVOLVE trial, and collected from the published literature and standard costing sources.

The rates of clinical events were estimated from the EVOLVE placebo group for each event of interest, that is, death, nonfatal CV event, nonfatal fracture, and parathyroidectomy (Table 2). For each event type, the person time was calculated from the randomization to the first occurrence of the event and censored at death or end of follow-up in the study (for the ITT analysis) or 6

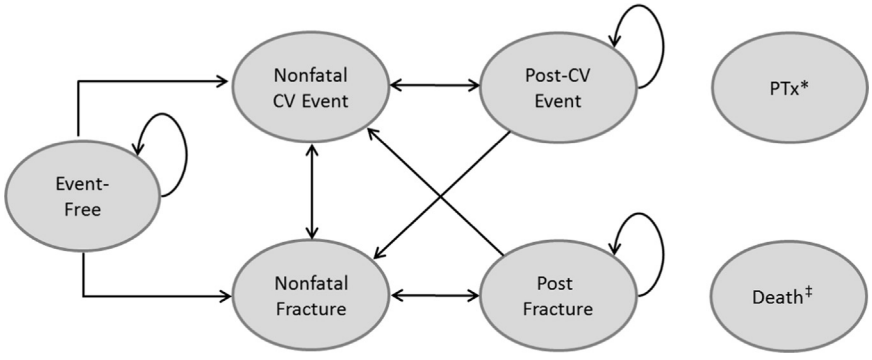

Fig. 1 – Model structure. *Notes.* **PTx costs and utility decrements are calculated outside the Markov by applying the expected costs, disutility, and probability of PTx to the number of patients alive. In the base-case analysis, PTx is treated as an outcome only (as in the EVOLVE trial) and is modeled outside of the Markov. This follows the statistical analysis of the EVOLVE trial in which PTx was not treated as a censoring event (e.g., CV and bone fracture events were counted post-PTx). The costs and utility decrements associated with the PTx surgery are applied to the per-cycle cost and QALY calculations. CV, cardiovascular; EVOLVE, EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events; PTx, parathyroidectomy; QALY, quality-adjusted life-year. *PTx was included in the model as an outcome that could be experienced in the event-free, nonfatal CV event, and nonfatal fracture event health states. ‡Patients may progress to the death health state from any other health state.**

Table 2 – Event rates, utilities, and cost inputs.

Annual event rates in conventional therapy, first (subsequent) event			Source
Health state	**ITT**	**Lag-censoring**	
All-cause death	0.10 (NA)	0.10 (NA)	[17]
Cardiovascular event*	0.08 (0.43)	0.10 (0.57)	[17]
Stroke	0.01 (0.01)	0.01 (0.01)	[17]
Bone fracture	0.04 (0.11)	0.04 (0.11)	[17]
Parathyroidectomy	0.05 (NA)	0.05 (NA)	[17]
Health state	**Utilities**		**Source**
Event-free	0.75		[43]
Cinacalcet	0.02		[43]
	Acute effect†	**Chronic effect†**	
Cardiovascular event*	0.19	0.14	[43]
Stroke	0.20	0.11	[43]
Bone fracture	0.31	0.12	[43]
Parathyroidectomy	0.06	0.00	[43]
Cost center	**Costs ($)**		**Source**
Cardiovascular event*	22,063		[7]
Stroke	21,618		[7]
Bone fracture	15,664		[7]
Parathyroidectomy	19,511		[40,41]
Cinacalcet	0.560/mg		[42]
Calcium acetate	0.001/mg		[42]
Sevelamer	0.004/mg		[42]
Lanthanum carbonate	0.008/mg		[42]
Calcitriol oral (IV)	3.060 (5.000)/μg		[42]
Doxercalciferol oral (IV)	8.620 (3.130)/μg		[42]
Paricalcitol oral (IV)	$10.270 ($3.030)/μg		[42]

EQ-5D, EuroQol five-dimensional questionnaire; EVOLVE, EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events; ITT, intent to treat; IV, intravenous; NA, not applicable/available.

* Myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event. Costs for cardiovascular events and fractures were calculated as a weighted average using the estimates from Lee et al [7]. for individual events and weights from the EVOLVE distribution of events in the ITT cohort. Costs inflated to February 2013 US dollars, using the medical component of the Consumer Price Index [23].

† Acute and chronic effects, i.e., reductions in utility, were estimated form the EQ-5D data in the EVOLVE trial using generalized estimation equations for the months 0 to 3, and for the months 4 to 12 after the event, [43].

months after discontinuation of the study drug (lag-censored analysis). The rate of subsequent events of each kind was estimated similarly in subjects who had an initial event of that kind. Naturalistic rates of the events in the US dialysis population were used as reported in the literature [11].

We assessed utilities for the health states using the EuroQol five-dimensional questionnaire (EQ-5D) data collected in the EVOLVE trial [43]. Patients were administered the EQ-5D instrument at baseline, and during the study visits at weeks 20, 52, 100, 148, 196, and 244. The EQ-5D data were also collected after a study-defined clinical event. The EQ-5D scores were converted to utilities on the basis of time trade-off responses from a representative sample of 2997 noninstitutionalized individuals in the United Kingdom [21]. We conducted a regression analysis to explain the EQ-5D utility using events as explanatory variables along with baseline utility score and an indicator variable for treatment group. Two different effects of events were considered (short-term and long-term). The short-term effect represents the disutility of an event within the first 3 months after the onset of the event, whereas long-term effects represent the disutility in all subsequent months postevent. The EQ-5D inputs for the model are summarized in Table 2 for the direct effects of cinacalcet and clinical events, and the full set of results from the regression analysis is presented in Appendix Table A1 in Supplemental Materials found at: http://dx.doi.org/10.1016/j.jval.2015.08.007. The model assumed half-recovery from the chronic effect beyond 1 year postevent.

We estimated health state costs for fatal and acute nonfatal CV events and fractures as the weighted average costs of the individual events that make up each category applied to published data from a claims analysis of costs for nonfatal CV events, fractures, and parathyroidectomies in the population with ESRD [7] (Table 2). Fatal CV event costs were based on the article by O'Sullivan et al. [22]. Acute costs described above are associated with a hospitalization directly after the event. Postevent costs capture costs associated with outpatient and nursing facility costs after hospital discharge. We modeled these costs for 9 months after the acute event. Costs were inflated to February 2013 US dollars, using the medical component of the Consumer Price Index [23].

Effect sizes were estimated from the EVOLVE data using proportional hazards models (Table 3). Because there was no clear effect modification by subsequent events in the repeated

Table 3 – Treatment effect estimates.

End point	Effect size as measured by hazard ratio (95% CI), cinacalcet vs. placebo		
	ITT unadjusted	ITT covariate-adjusted*	Lag-censoring*
All-cause death	0.94 (0.85–1.04)	0.87 (0.78–0.97)	0.80 (0.69–0.91)
CV event†	0.86 (0.76–0.98)	0.85 (0.74–0.97)	0.78 (0.67–0.91)
Stroke	1.07 (0.82–1.40)	1.07 (0.79–1.45)	0.95 (0.67–1.36)
Bone fracture	0.89 (0.75–1.07)	0.86 (0.72–1.04)	0.73 (0.59–0.92)
Parathyroidectomy	0.44 (0.36–0.54)	0.42 (0.34–0.51)	0.25 (0.19–0.33)

CI, confidence interval; CV, cardiovascular; HDL, high-density lipoprotein; ITT, intent to treat.
* 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, HDL, calcium-phosphate product (CaxP), and albumin.
† Myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event.

event analysis [17], we applied the same treatment effects to first events as well as to subsequent events.

We used parametric survival models to project posttrial survival and rates of clinical events. The model fits were assessed using Akaike information criterion and tested qualitatively for the external validity on the basis of the expected survival over the lifetime. We used published literature estimates for mortality rates in general dialysis population between 23.0 per 100 patient-years [24] and 26.6 per 100 patient-years reported in reference [25]. Based on the Akaike information criterion statistics and on the projected survival beyond the trial, the Weibull distribution was best fit for the lifetime projections. Model fit coefficients for the survival analysis on the mortality input are summarized in Appendix Table A2 in Supplemental Materials found at: http://dx.doi.org/10.1016/j.jval.2015.08.007. A scenario analysis was conducted to address the issue of differences in event rates.

Comedications and Treatment Discontinuation

The use and doses of comedications for sHPT are summarized in Appendix Table A3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.007. Comedications were tracked prospectively—the doses of vitamin D were recorded directly from the trial. Phosphate binders were tracked in the trial as a type of binder; we estimated the dose using the maximum recommended doses for product labels. Not all patients received vitamin D sterols; therefore, costs are calculated only for those receiving vitamin D sterols. In the first year, 74.2% of the patients randomized to cinacalcet and 77.3% of the patients randomized to placebo group received vitamin D sterols. Similarly, by averaging subsequent years of treatment (years 2+), 73.3% and 81.6% of the patients, respectively, received vitamin D sterols.

We modeled treatment discontinuation from cinacalcet by applying the annual probability of discontinuation as seen in the EVOLVE trial, that is, 27.3%. Because 19.8% of the subjects randomized to the placebo group started commercial cinacalcet at some point during the trial, we tested the model sensitivity to the inclusion of these costs in scenario analyses.

Perspectives and Analyses

The model assumes the perspective of a third-party payer (e.g., a managed care organization in the United States). We considered only direct medical costs, that is, costs related to cinacalcet and other sHPT medication use, and costs due to CV events, fractures, and parathyroidectomies. Outcomes were valued in terms of incremental life-years and QALYs. The cost-effectiveness was assessed in terms of incremental cost-effectiveness ratio (ICER) per life-year gained and per QALY gained.

Using the event rates estimated from the EVOLVE ITT analysis and assuming that treatment effects observed in the trial were attenuated beyond the trial period proportionately to treatment discontinuation, we assessed the cost-effectiveness of cinacalcet using clinical effect estimates from the covariate-adjusted ITT analysis and unadjusted ITT analysis.

We further conducted a range of scenario analyses using effect estimates from the covariate-adjusted ITT analysis: 1) used treatment effect estimated from the lag-censoring analysis; 2) assumed full treatment effects for the lifetime; 3) assumed treatment effect for the duration of the trial only; 4) used naturalistic event rates from the US dialysis population (see Appendix Table A4 in Supplemental Materials found at: http://dx.doi.org/10.1016/j.jval.2015.08.007); 5) excluded costs of commercial cinacalcet from the placebo group; 6) assumed beneficial effect of parathyroidectomy on the clinical events of 10% and [6] 20%; 7) included stroke in the definition of the CV event state; and 8) included the cost of commercial cinacalcet in patients who reinitiate cinacalcet in the active arm after discontinuation (there were a total of 222 subjects who reinitiated commercial cinacalcet in the cinacalcet arm, or a reinitiation rate of 3.7%, and we modeled this scenario by *reducing* the discontinuation rate of cinacalcet of 27.3% by that amount, i.e., to be 23.6%), and 10) included dialysis costs to represent limited societal perspective.

In addition to the scenario analyses, we conducted a one-way sensitivity analysis in which the model input parameters were varied individually using reasonable lower and upper bounds of each parameter, that is, 95% confidence limits for the estimated parameters, and ±20% variation on the list price of cinacalcet. Last, we performed a second-order Monte-Carlo probabilistic sensitivity analysis to evaluate the impact of simultaneous variation in clinical outcomes and resource utilization parameters (for the sampling distributions, see Appendix Table A5 in Supplemental materials found at http://dx.doi.org/10.1016/j.jval.2015.08.007) on the model results and presented the results as cost- effectiveness acceptability curves for each of the scenario analyses.

Results

Table 4 summarizes the results of the analyses over the lifetime for treatment effect estimates from the covariate-adjusted and unadjusted ITT analyses. In each treatment effect estimate, cinacalcet therapy was associated not only with increased life-years (0.55, 0.25) and QALYs (0.42, 0.23) but also with increased lifetime costs ($33,809, $27,114). The respective ICERs were $79,562 and $115,876 per QALY.

Table 5 summarizes results of the additional scenario analyses around covariate-adjusted ITT treatment effect estimates. The results are presented in the order of increasing (less favorable) cost-effectiveness. Using the assumptions of the full treatment effect beyond the duration of the trial decreased the

Table 4 – Results of the model simulation for the adjusted and unadjusted ITT effect estimates.

Costs and outcomes	ITT, covariate-adjusted			ITT, unadjusted		
	Cinacalcet	Conventional therapy	Difference	Cinacalcet	Conventional therapy	Difference
Cost category ($)						
Cinacalcet	51,944	5,068	46,875	50,350	5,068	45,282
Usual care	97,281	103,874	–6,592	93,743	103,874	–10,131
CV-related	57,512	60,253	–2,741	56,104	60,253	–4,149
Fracture-related	10,121	10,401	–280	9,918	10,401	–483
PTx-related	2,838	6,291	–3,453	2,886	6,291	–3,405
Total	219,696	185,887	33,809	213,001	185,887	27,114
Outcome category						
LYs gained	8.14	7.59	0.55	7.84	7.59	0.25
QALYs gained	5.47	5.04	0.42	5.28	5.04	0.23
ICER per LY gained			61,705			107,691
ICER per QALY gained			79,562			115,876

Note. Costs and outcomes are discounted at 3% per year; costs inflated to February 2013 US dollars, using the medical component of the Consumer Price Index [23].
CV, cardiovascular; ICER, incremental cost-effectiveness ratio; ITT, intent to treat; LY, life-year; PTx, parathyroidectomy; QALY, quality-adjusted life-year.

ICER to $63,147 per QALY, respectively. More conservative assumption of limiting cinacalcet effect to the duration of the trial increased the ICER to $98,220 per QALY. Including stroke, applying naturalistic event rates to the conventional therapy group, and assuming a 10% beneficial effect of parathyroidectomy had a small worsening effect on the ICER, moving it up to approximately $83,000 per QALY. The assumption of the 20% positive effect of parathyroidectomy and exclusion of the commercial cinacalcet costs in the conventional therapy group had somewhat more pronounced worsening effect, moving the ICER to approximately $89,000 per QALY. Including the cost of commercial cinacalcet in the cinacalcet group did not materially change the ICER ($79,711 per QALY). The inclusion of dialysis costs in the analysis substantially increased the ICER to $191,072 per QALY.

With lag-censoring effect estimates, the ICER was $56,686 per QALY.

Results of the one-way sensitivity analyses are summarized in the form of a tornado diagram in Figure 2, which shows the five most sensitive parameters in the model. Overall, model results were most sensitive to the effect estimates for survival, the cost of cinacalcet, followed by effects on fracture, cinacalcet-related utility, and CV death.

Results of a probabilistic sensitivity analysis indicated that for most of the simulated scenarios, the ICER was less than $100,000 per QALY in more than 60% of the simulation runs. In the scenarios in which treatment effect is limited to trial duration only or in which the unadjusted ITT effect estimates are assumed, the proportions of simulation runs with ICER less than $100,000 per QALY are 48% and 39%, respectively. Inclusion of dialysis costs produces an ICER of less than $100,000 per QALY in only 2% of the simulation runs. Results of the probabilistic sensitivity analyses are presented as cost-effectiveness acceptability curves (Fig. 3) in which costs per incremental QALYs are plotted on the X axis and the probability of being cost-effective is plotted on the Y axis, with the plots arranged in the order of decreasing probability of cinacalcet being cost-effective.

Discussion

We conducted a cost-effectiveness analysis of cinacalcet using data from the EVOLVE trial, taking the US health care perspective, in which the ICER was sensitive to treatment effect estimates; that is, using the covariate-adjusted ITT analysis and unadjusted ITT analysis, the ICER was $79,562 and $115,876 per

Table 5 – Results of the model simulation: Scenario analyses.

Simulation scenario	ΔLY	ΔQALY	ΔCost ($)	ICER per LY	ICER per QALY ($)
Lifetime treatment effect	0.82	0.59	37,413	45,711	63,147
Include commercial cinacalcet cost in the cinacalcet arm	0.55	0.42	33,987	62,030	79,711
Include stroke	0.55	0.43	34,655	63,249	81,026
Naturalistic event rates	0.46	0.38	31,647	68,610	83,169
PTx improves outcomes by 10%	0.50	0.40	33,341	66,190	83,547
PTx improves outcomes by 20%	0.46	0.37	32,827	72,126	88,564
Exclude commercial cinacalcet cost from the placebo arm	0.55	0.43	38,877	70,955	89,916
Study duration treatment effect only	0.40	0.35	34,210	86,170	98,220
Include dialysis costs	0.55	0.42	81,194	148,188	191,072

Note. Costs inflated to February 2013 US dollars, using the medical component of the Consumer Price Index [23].
ICER, incremental cost-effectiveness ratio; LY, life-years; PTx, parathyroidectomy; QALY, quality-adjusted life-year.

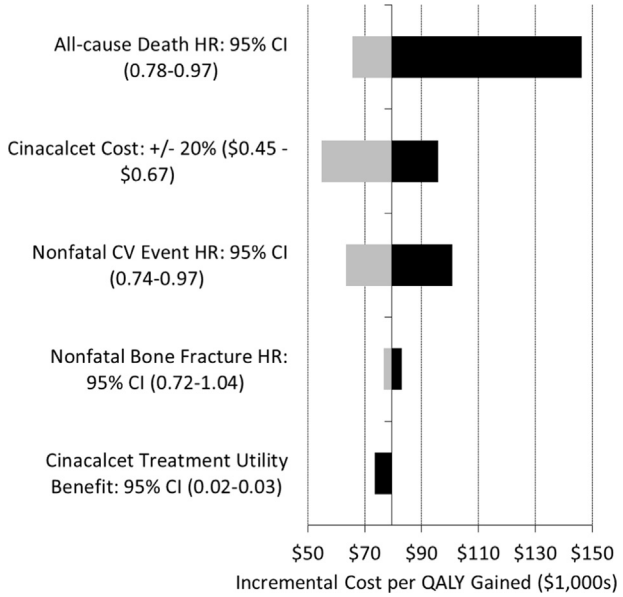

Fig. 2 – One-way sensitivity analysis. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; QALY, quality-adjusted life-year.

QALY, respectively. This is consistent with an earlier cost-utility analysis in the United States that extrapolated data from observational studies [11] and reported the ICER in the range of $54,000 to $75,000 per QALY. Our results being slightly higher are likely explained by the changes in cinacalcet price over time, and a higher dose of cinacalcet in our analysis than in previous studies.

The unique strength of our analysis is that it is based on a randomized controlled trial that directly assessed the effect of cinacalcet therapy on clinical outcomes. Although the result of the primary analysis of the EVOLVE trial—an unadjusted ITT analysis—was not statistically significant, treatment effect estimates were influenced by imbalance in age at randomization and high rates of discontinuation of study drug in both cinacalcet and placebo groups. We used effect estimates from unadjusted ITT analysis and prespecified lag-censoring and covariate-adjusted ITT analyses to inform treatment effect inputs for our model. Using covariate-adjusted ITT analysis allowed adjustment for potential confounders at randomization and improved internal validity of the treatment effect estimates. Patients with sHPT on dialysis range from very young to very old; that is, the SD of age in this population is large compared with most other large outcome studies in patients with other CV disease in which the age range of the population is narrower. Other large randomized controlled trials have shown changes in effect estimates after adjustment for unexpected differences in baseline determinants of risk [26–28]. Although the ITT principle in general should represent the least biased measure of the treatment effect, imbalance in age at randomization in the EVOLVE trial makes the covariate-adjusted ITT analysis less biased than the unadjusted analysis.

Importantly, we approached this analysis from the estimation, rather than a hypothesis testing, standpoint as recommended in Briggs and O'Brien [29], quantifying uncertainty surrounding the ICER and presenting results as cost-effectiveness acceptability curves. If one wished to assume zero benefit of cinacalcet on the basis of the nonsignificant *P value* in the trial's primary (unadjusted ITT) analysis, the incremental cost of cinacalcet therapy can be read directly from Table 3, that is, additional $46,875 over lifetime.

The results of our economic model were most sensitive to the treatment effect estimates, particularly the effects on survival: treatment effect on mortality ranked as the highest influential input parameter in the one-way sensitivity analysis. This is not surprising for a lifetime economic analysis, and similar observations were made by others [30]. This effect was further evidenced by the ICER of approximately $56,000 per QALY and the ICER of approximately $116,000 per QALY associated with assumptions of the lag-censoring effect estimates (20% improvement in mortality) and the unadjusted ITT effect estimate (6% improvement in mortality). The lag-censoring analysis assumes adherence to cinacalcet and is therefore not fully representative of the real world in which adherence to cinacalcet and other oral drugs is known to decrease over time [31]. Excluding costs of commercial cinacalcet from the conventional therapy arm increased the ICER to approximately $90,000 per QALY, highlighting the sensitivity of the model to the overall costs of cinacalcet, which was also seen as one of the major sources of variance in the one-way sensitivity analysis, whereas including stroke (an important outcome not included in the primary composite end point of EVOLVE) did not materially change the ICER.

Previous studies highlighted potential advantages of parathyroidectomies in terms of cost-effectiveness as compared with pharmacotherapies [16,32]. The patient population in EVOLVE was that with moderate-to-severe sHPT, and the median level of PTH was 693 pg/ml. Surgery or medical therapy are both acceptable methods of management of sHPT. Given the fact that most patients on hemodialysis are considered to be at a relatively high surgical risk, most patients are treated medically, and surgical therapy is generally reserved for patients who are refractory to medical therapy. Severe unremitting HPT occurred frequently in the EVOLVE trial despite conventional therapy and cinacalcet substantially reducing its occurrence [33]. Therefore, consistent with the EVOLVE trial design, we modeled parathyroidectomies as outcomes, rather than as treatment comparators. We then explored scenarios in which parathyroidectomies confer beneficial effects on the outcomes. Because randomized trials of

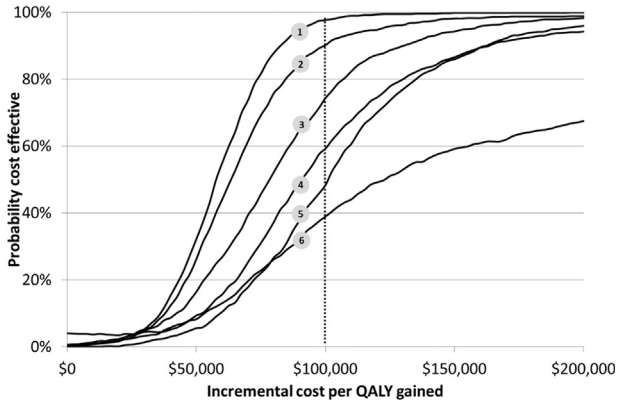

Fig. 3 – Cost-effectiveness acceptability curves for scenario analyses. Probabilistic sensitivity analyses and probability of being cost-effective at $100,000 per QALY: 1) Lag-censored effect size (97.7%), 2) lifetime full effect (90.2%), 3) adjusted ITT effect size (73.2%), 4) PTx improves outcomes by 20% (59.3%), 5) effects limited to the trial duration (48.4%), 6) unadjusted ITT effect size (39.0%). Curves not shown for the following scenarios: Include stroke (72.6%), PTx improves outcomes by 10% (68.5%), naturalistic rates in the comparator arm (68.2%), exclude commercial cinacalcet costs (64.4%), including dialysis costs (2.0%). ITT, intent to treat; PTx, parathyroidectomy; QALY, quality-adjusted life-year.

parathyroidectomies versus pharmacotherapies have not been conducted, and effects from observational research can be biased, we made an assumption of 10% and 20% improvement in the study outcomes postparathyroidectomy, which led to the increase of the ICER to approximately $83,000 and $88,000 per QALY.

Another aspect of our work that sets it apart from other cost-effectiveness analyses of cinacalcet, and many other medications used in dialysis, is the accuracy and precision of the utility estimates. The analysis of the EVOLVE EQ-5D data informs the current economic model [43]. Thus, the utility inputs were assessed for this specific population, for the specific events on interest, including short-term and long-term effect, and also estimating the direct effect of treatment. We did not explicitly model adverse events because the related adverse events of cinacalcet (principally nausea and vomiting) are considered relatively minor and not costly. Their impact on patients is implicitly included in the analysis of utilities. Because of the positive, albeit small, overall beneficial effect of cinacalcet on health-related quality of life, we believe that symptom relief due to cinacalcet [34] probably outweighs or at least balances any potential short-term effects of adverse events.

The final scenario included the cost of providing dialysis. This approach reflects a limited societal perspective as discussed by Russell et al. [35], that is, in which all costs and benefits, irrespective of who incurs them, should be included in the analysis. All other assumptions are consistent with the recommendations for societal perspective, including valuing all health effects; using community-based utility weights; and discounting costs and effects. We did not include costs due to productivity loss because most of the patients undergoing dialysis are not working or elderly [36]. Opportunity cost is often approximated by the market price, although some argue that patent protection laws distort markets and hence a discounted (40%–60%) price would represent a more accurate opportunity cost [37]. To be conservative, we used the market price (red book) as the measure of opportunity costs. The limited societal perspective can serve as a reference case to compare cost-effectiveness across programs, but the practical utility of inclusion of dialysis costs in such an analysis is debatable because cinacalcet is intended for the treatment of sHPT and not for the underlying ESRD. Because dialysis is an expensive procedure with annual Medicare expenditure on hemodialysis of $87,945 [25], the life-years gained would incur additional lifetime costs because of prolongation of dialysis treatment, and thus would likely bias the results against any life-extending treatment of patients receiving dialysis. In terms of making resource allocation decisions, this would mean that patients requiring dialysis could be denied access to life-extending therapies simply because dialysis is costly [38]. This point of view is shared by others conducting cost-effectiveness analyses in the dialysis population [11,30].

We conducted extensive probabilistic sensitivity analyses on top of each scenario. Assuming that the efficacy estimates from covariate-adjusted ITT analysis represent in this case the least biased and most relevant estimate, the results of the probabilistic sensitivity analyses suggest a high probability (60%–80%) of cost-effectiveness using the willingness-to-pay threshold of $100,000 per QALY [39]. The results for the unadjusted ITT analysis had 39% probability to be cost-effective, consistent with lower estimated effects on outcomes.

An important limitation of our study is the heterogeneity of the patient population in the EVOLVE trial as it is applied for the economic assessment from the US perspective. Important regional variations in age (i.e., younger patients in Latin America and Russia than in the United States) increase generalizability, but may slightly bias results as they pertain to patients in the United States. We have addressed this by applying naturalistic event rates from the US dialysis population to the conventional therapy group leading to a very slight change in the ICER, suggesting that the EVOLVE trial was not unduly biased by the ex-US subpopulations, which is not surprising considering that 37% of the subjects were from the United States and 75% were from Western countries with comparable demographic characteristics. This mix of younger patients (who tend to have more severe sHPT, thereby qualifying for enrollment), together with the "healthy clinical trial participant effect," may explain the difference in survival observed within the EVOLVE trial in comparison to the general hemodialysis population. We used covariate-adjusted treatment effects from the EVOLVE trial for the naturalistic event rates scenario because the observed efficacy should apply directly to the general hemodialysis population as there was no biologically plausible interaction of treatment effect by covariates. There was some imprecision in estimating the costs of concomitant medications for sHPT because we did not collect information on the dose of phosphate binders. Cinacalcet, however, tends to lower serum phosphate concentrations relative to conventional therapy (vitamin D sterols); therefore, a change in the dose of phosphate binders was unlikely to yield a material increase in costs in the cinacalcet group. We did not explicitly model adverse reactions, which for cinacalcet may include, most frequently, nausea, vomiting, and diarrhea [10]; because these events are not costly and their impact on QALYs would be expected to show in our utility analysis, we think that this approach is reasonable. General limitations of Markov assumptions, that is, lack of memory, apply to our analysis, which we have tried to address by keeping track of the event counts outside of the Markov process. Despite limitations of the Markov approach, we feel that its structure and process allowed a balance between the ease of understanding and the complexity of sHPT and its treatments.

In conclusion, the choice of treatment effect estimates used in our model materially influenced the cost-effectiveness of cinacalcet. In the unadjusted ITT analysis, cinacalcet does not represent a cost-effective use of health care resources when applying a willingness-to-pay threshold of $100,000 per QALY. When using the covariate-adjusted ITT treatment effect, which represents the least biased estimate, however, cinacalcet is a cost-effective therapy for patients on hemodialysis with moderate-to-severe sHPT.

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Supplemental Materials

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