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ORIGINAL RESEARCH

The cost-effectiveness of extended-release calcifediol versus paricalcitol for the treatment of secondary hyperparathyroidism in stage 3–4 CKD

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ABSTRACT

Aims: Patients with chronic kidney disease (CKD) not on dialysis frequently have vitamin D insufficiency (VDI) and secondary hyperparathyroidism (SHPT), which are associated with an increased risk of cardiovascular (CV) disease, fracture, CKD progression, and death. This study estimated the cost-effectiveness of extended-release calcifediol (ERC) vs paricalcitol for the treatment of patients with CKD stages 3–4 that have SHPT and VDI.

Materials and methods: An economic analysis of SHPT treatments among a hypothetical cohort of 1,000 patients with CKD Stage 3 and 4 with SHPT and VDI was developed to estimate differences in the rates and costs of CV events, fractures, CKD stage progression, and mortality in patients treated with ERC and paricalcitol. A Markov model was developed with 1-year cycles and a 5-year time horizon from a US Medicare payer perspective with costs valued in 2017 US dollars.

Results: The outcomes of the model were rates of clinical events, total costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). Across a 1,000-person cohort, ERC was the dominant (less costly, more effective) treatment strategy when compared with paricalcitol. Treatment with ERC resulted in cost savings of $14.8 M (95% CI = −$10.0 M–$45.2 M) and an incremental gain of 340 QALYs (95% CI = 200–496) compared to treatment with paricalcitol.

Limitations: Bridging biochemical levels to clinical outcomes may not represent real-world risk of the clinical events modeled. Future real-world outcomes of patients treated with ERC and paricalcitol may be used to evaluate the model results.

Conclusions: This model demonstrated favorable short- and long-term clinical benefits associated with the use of ERC in patients with CKD Stage 3 and 4 with SHPT and VDI, suggesting ERC may be cost-effective from the Medicare perspective compared to paricalcitol.

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Introduction

An estimated 30 million people, ~15% of all adults in the United States, have chronic kidney disease (CKD), including one in three adults with diabetes and one in five adults with high blood pressure[1]. The severity of CKD is measured in five stages defined by the estimated glomerular filtration rate (eGFR), where stage 1 is the least severe with minimal complications and stage 5 is the most severe (see Table 1 for classification of CKD stages based on eGFR). The progression of CKD is associated with poor clinical outcomes[2–4].

Secondary hyperparathyroidism (SHPT) refers to the excessive secretion of intact parathyroid hormone (iPTH) by the parathyroid glands and is a common complication of CKD. Elevated iPTH levels are associated with an increased risk of cardiovascular (CV) events[5], including congestive heart failure and acute myocardial infarction, as well as loss of bone mineral density (BMD) and debilitating fractures[6–8]. Vitamin D insufficiency (VDI), defined as serum total 25-hydroxyvitamin D levels less than 30 ng/mL (75 nmol/L), can also develop early in CKD, and its prevalence increases with CKD progression. Vitamin D regulates plasma levels of iPTH via the vitamin D receptor in the parathyroid glands and promotes the intestinal absorption of calcium; therefore, VDI contributes to high bone turnover, SHPT, and decreased BMD in CKD[9]. Patients with CKD with SHPT or VDI are at increased risk of death and progression to a later disease stage requiring dialysis.

Treatment of SHPT and VDI prior to dialysis is often under-valued, and these conditions are not adequately treated during the early stages of CKD despite patients not meeting iPTH target levels established in the K/DOQI guidelines[10]. It is important to manage SHPT and VDI early in CKD in order to reduce the risk for progression to dialysis/end-stage renal disease (ESRD). Because of the high costs associated with the management of ESRD, early treatment may offset costs associated with healthcare utilization in later disease stages due to fewer patients reaching progressing to ESRD.

Extended-release calcifediol (ERC; Rayaldee, Opko, Miami, FL) is a newly approved prohormone of the active form of

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vitamin D_3 (calcitriol or 1,25-dihydroxyvitamin D_3) indicated for the treatment of SHPT in patients with CKD not on dialysis who have VDI[11]. ERC requires *in vivo* activation to stimulate vitamin D responsive pathways. Randomized clinical trials have demonstrated that ERC reduces iPTH and increases 25(OH)D simultaneously in patients with CKD. This finding impacts the current and future treatment landscape for SHPT given that current treatments do not adequately address both 25(OH)D and iPTH levels despite the unmet need[12]. Furthermore, recently updated KDIGO Clinical Practice Guideline do not recommend the routine use of calcitriol and active vitamin D analogs in patients with CKD stages 3–5 not on dialysis due to the increased risk of hypercalcemia[13]. In clinical trials, ERC gradually elevated serum 25(OH)D to within the normal laboratory range and allowed effective suppression of elevated iPTH in patients with SHPT, stage 3 or 4 CKD, and vitamin D insufficiency with minimal effect on serum levels of calcium and phosphorus[14].

In this study, we evaluated the cost-effectiveness of ERC from a US Medicare payer perspective utilizing data from the Phase 3 clinical trial of ERC[15]. The comparator chosen for the analysis was paricalcitol, an established vitamin D analog indicated for the treatment of SHPT in patients with CKD who are not on dialysis. The primary outcome in the paricalcitol trial was iPTH levels.

Table 1. Classification of CKD based on eGFR.

CKD stage	Description of kidney function	eGFR (ml/min/1.73 m^2)
1	Normal or high	≥90
2	Mildly decreased	60–89
3a	Mildly to moderately decreased	45–59
3b	Moderately to severely decreased	30–44
4	Severely decreased	15–29
5	Kidney failure	<15

Abbreviations. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Adapted from KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2017;7:1–59.[13]

Methods

Study design

The cost-effectiveness analysis estimated the clinical and economic consequences of treatment with ERC in comparison to treatment with paricalcitol for patients with CKD stages 3 and 4 with SHPT and VDI. Drug costs of ERC and paricalcitol are contrasted with reduced rates of CV events, fractures, and CKD progression and the associated cost savings.

Model structure

The Microsoft Excel model uses a decision tree and Markov model with a 5-year time horizon and a 1-year cycle length. The model is used to perform a Monte Carlo simulation of a hypothetical cohort of 1,000 patients with stage 3 and 4 CKD. The three stages of the Markov model include: patient stays in original CKD stage, patient progresses to the next CKD stage, and patient death. Patients' transition between disease states through the time horizon and each state is accompanied by utilities associated with that state. The model also allows for the assessment of rates of cardiovascular events, fracture events, CKD stage progression, other adverse events, and costs of treatment at each step. A diagram of the Markov model is illustrated in Figure 1.

Because the average age of patients with CKD stages 3 and 4 is 68 and 67 years, respectively[16], a US Medicare payer perspective was taken to reflect the benefits and consequences that are relevant to this population. Costs and outcomes were discounted at a rate of 3% annually, as recommended by both the US Office of Management and Budget[17] and the Public Health Service Panel on Cost-Effectiveness in Medicine[18]. One-way deterministic sensitivity analyses varied inputs by standard deviations or confidence intervals provided in the source literature or by ±25% when standard deviations or standard errors were not available. We also performed a probabilistic sensitivity analysis.

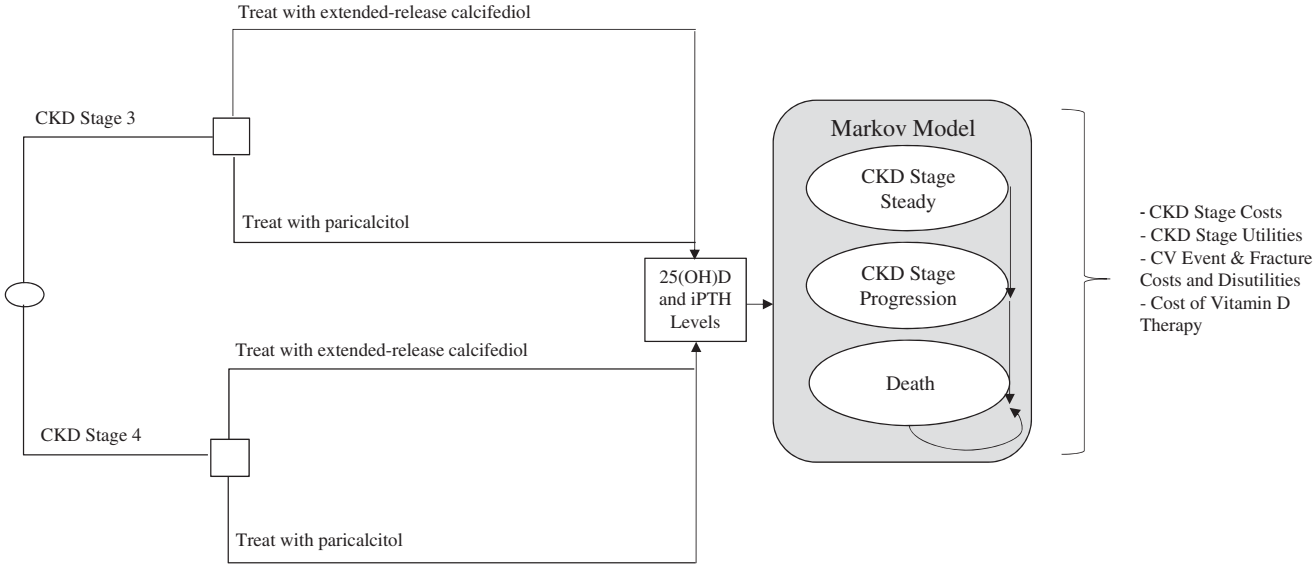

Figure 1. Markov model conceptual diagram.
Abbreviations. CKD, chronic kidney disease; iPTH, intact parathyroid hormone.

Table 2. Baseline cohort demographics.

	CKD stage 3	CKD stage 4	Source
% of Cohort	81.5%	18.5%	16
Age	68	67	13
% Female	24.7%	43%	13
Mean 25(OH)D levels (95% CI)	23.3 (8.8–37.8)	18.6 (5.3–31.9)	17
Mean iPTH levels (95% CI)	114.0 (39.0–189.0)	235 (0.0–470.0)	17

Abbreviations. 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; CKD, chronic kidney disease; iPTH, intact parathyroid hormone.

Table 3. Baseline risk of CV events and fracture.

	Input value	Source
Baseline rate of clinical events		
CV event, percentage		21
Stage 3	7.5	
Stage 4	21.8	
Stage 5	36.6	
Fracture, percentage		24
Stage 3	0.6	
Stage 4	0.8	
Stage 5	1.0	
Rate of CKD progression, percentage		20
Stage 3 to 4	19	
Stage 3 to 5	6	
Stage 4 to 5	27	
Risk of clinical event based on changes in 25(OH)D		
CV event, RR (95% CI)	0.56 (0.35–0.91)	23
Risk of fracture per 1 SD increase in BMD, OR (95% CI)†	0.57 (0.45–0.77)	25
CKD Progression from Stage 3, RR	0.57 (0.36–0.89)	27
CKD Progression from Stage 4, RR	0.69 (0.53–0.90)	
Mortality*, HR	0.76 (0.56–1.05)	
Risk of clinical event based on changes in iPTH		
CV event, RR	0.27 (0.13–0.59)	22
Risk of fracture per 1 SD increase in BMD, OR (95% CI)†	0.57 (0.45–0.77)	25
CKD stage progression per 51–110 pg/mL change in iPTH on CKD stage progression, HR	2.15 (0.97–4.76)	28
CKD stage progression per 111–199 pg/mL change in iPTH on CKD stage progression, HR	5.24 (2.48–11.10)	
Mortality per 51–110 pg/mL change in iPTH, HR	0.91 (0.64–1.30)	
Mortality per 111–199 pg/mL change in iPTH, HR	1.83 (1.29–2.59)	

Abbreviations. CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; iPTH, intact parathyroid hormone; OR, odds ratio; RR, risk ratio; SD, standard deviation.
*Hazard ratio measuring baseline risk of mortality amongst patients with CKD. This value is applied to the baseline risk of death among health patients. †Includes hip and vertebral fracture.

Characteristics of the hypothetical 1,000 patients with CKD stages 3 and 4 were obtained from the literature and summarized in Table 2. The characteristics of the cohort are used to calculate weighted averages of treatment effects by stage[19] as well as rates of CV events, fractures, CKD progression, and mortality. Baseline 25(OH)D and iPTH levels among the cohort were identified in the literature and stratified by CKD stage[20]. The efficacy of ERC on 25(OH)D and iPTH outcomes was determined by the phase 3 pivotal trials[15]. Paricalcitol outcomes on iPTH were taken from phase 3 pivotal trials, while data on 25(OH)D outcomes were taken from a separate randomized, placebo-controlled clinical trial due to the exclusion of 25(OH)D measurement in the pivotal trials[21,22]. The changes observed in both parameters were applied to the baseline 25(OH)D and iPTH levels.

Transition probabilities

The baseline stage transition rates were obtained from the literature[23]. CKD treatment-modified stage progression and transition through the model are affected by the incremental changes in 25(OH)D and iPTH levels associated with each treatment.

Risk parameters

Baseline risk of CKD stage transition, mortality, CV events, and fractures were obtained from the literature (Table 3). Risk ratios (RR), odds ratios (OR), and hazard ratios (HR) were used to compare ERC with paricalcitol. These ratios were applied to the baseline stage transition, mortality, CV event, and fracture risk profiles to create the treatment-modified risk rates. Levels of 25(OH)D and iPTH were associated with the risk of each clinical event analyzed. Incremental benefits associated with changes in 25(OH)D and iPTH levels as a result of ERC or paricalcitol therapy are accounted for in the model.

The number of CV events in each treatment group per 1-year cycle was calculated by multiplying the natural history risk rate by stage[24] by the treatment-modified risk ratio and by the remaining number of patients in the cohort after CKD stage 5 progression discontinuation and dropout. The RR in the literature for any CV event associated with vitamin D therapy (VDT) is an aggregate mean RR; therefore, this RR was applied to all stages[25]. The RR for a CV event associated with a 2.72-fold increase in 25(OH)D levels was 0.56[26], and each 50 pg/mL reduction in iPTH is associated with a RR of 0.77[27].

Natural history baseline fracture rates were obtained from the literature, stratified by sex and age. Weighted average risk ratios were calculated based on inputs for cohort age and sex, which were taken from the baseline demographics presented in Table 2. An OR of 0.57 is associated with every 1 standard deviation increase in BMD[28]. This OR was bridged to calculate an OR for hip or lumbar spine fracture, given VDT[29]. This calculated OR was then converted to an RR of 0.92. The method used to calculate fracture rates due to change in 25(OH)D levels was also used to calculate hip fracture rates associated with changes in iPTH.

A 10-ng/mL increase in 25(OH)D is associated with an HR of 0.57 in CKD stage 3 and an HR of 0.69 in stage 4[30]. The efficacy data for ERC and paricalcitol was applied to the RR such that an incremental risk reduction is conferred to patients based on the changes in 25(OH)D levels. For iPTH, there is an HR (range = 2.15–13.17)[31] associated with stage progression per 50 pg/mL increase in a patient's iPTH level. Because these HRs are categorical, an HR was assigned based on the absolute level of iPTH after treatment as opposed to applying an incremental change.

Mortality rates for patients were calculated by combining mortality risk by CKD stage and annual all-cause mortality rates from US Life Tables. Mortality is treatment-modified through the mechanism of change in CKD stage progression.

Costs

Cost inputs are summarized in Table 4. All drug and medical costs were converted to September 2017 US dollars using the Medical Care component of the Consumer Price Index[32]. Drug costs for ERC and paricalcitol were obtained from Red Book (January 2018) using the branded wholesale acquisition cost (WAC)[33]. Costs of CV events, fractures, and stage progression were obtained from the literature[34–36].

Table 4. Drug and clinical event costs.

Cost category	Cost (2017 USD)	Source
ERC WAC gross annual cost, label dosing	$11,136	10
Paricalcitol WAC gross annual cost, label dosing	$4,684	18
CKD stage III	$21,440	29
CKD stage IV–V	$32,116	29
ESRD	$93,113	30
Any CV event	$26,454	28
Hip fracture	$28,227	28

Abbreviations. CKD, chronic kidney disease; CV, cardiovascular; ERC, extended-release calcifediol; ESRD, end-stage renal disease; USD, United States dollars; WAC, wholesale acquisition cost.

Utilities

Health-related quality-of-life information was obtained from the literature. Utility values by CKD stage are shown in Table 5. The utility values were estimated using the time-trade off method and were multiplied by the number of patients alive in each stage at the end of the 1-year cycle to calculate the QALY[37]. The model also included CV event and fracture disutility in the QALY calculations[38].

Sensitivity analyses

Probabilistic and one-way sensitivity analyses were conducted to examine how changes to key inputs would affect the results. The one-way sensitivity analyses measured the sensitivity of the annual drug costs (ERC and paricalcitol), clinical costs (CV event, fracture, Stage 5/ESRD), efficacy on 25(OH)D outcomes, and 25(OH)D treatment-modified RRs for CV events and CKD progression.

In the probabilistic sensitivity analysis (PSA), all of the key study parameters including all drug costs, clinical event costs, baseline clinical event rates, treatment modified clinical event risk, and drug efficacy were sampled from parametric distributions given the point estimates and 95% confidence intervals or standard deviations reported in the literature. Parameters with unavailable measures of spread were varied by ±25% of the point estimate. The model runs 1,000 simulations.

Results

The key outcomes of the analysis include total costs, difference in clinical events, quality-adjusted life years (QALYs), and the incremental cost-effectiveness (ICER) of ERC compared to paricalcitol. The total costs associated with ERC and paricalcitol include the total drug costs and clinical event costs associated with stage progression, CV events, and fractures. Clinical outcomes were estimated as the difference in total CV events, fractures, patient-years in CKD Stage 5, life years gained, and deaths averted over the 5-year time horizon.

Clinical outcomes

The clinical outcomes were favorable for ERC when compared with paricalcitol. The ERC cohort experienced 145 fewer CV events (95% CI = −78–489), spent 423 fewer years in CKD stage 5 (95% CI = 208–617), gained 315 life years (95% CI = 142–516), and avoided 92 deaths (95% CI =

Table 5. Utility values by CKD stage.

	Time trade-off (SE)	HUI-3 global utility (SE)	Source
Utility level for Stage III patients	0.87 (0.24)	0.67 (0.31)	34
Utility level for Stage IV patients	0.85 (0.23)	0.55 (0.34)	34
Utility level for Stage V/ESRD patients	0.72 (0.37)	0.54 (0.31)	35
Disutility for CV event*	−0.14 (0.21)		35
Disutility for fracture†	−0.09 (0.16)		35

Abbreviations. ESRD, end-stage renal disease; HUI, Health Utilities Index; SE, standard error.
*Average disutility of CV events, including MI, angina, heart failure, and stroke.
†Average disutility of arm and hip fracture.

Table 6. Total costs and QALYs for ERC and paricalcitol, 1,000 patients, 5 years.

	Extended-release calcifediol	Paricalcitol	Difference	95% CI*
Treatment Efficacy				
Change in serum 25(OH)D (ng/mL)	47.4	−6.7	—	
Change in iPTH (pg/mL)	−31.9	−104	—	
Clinical Outcomes				
CV events, Disc.	2,211	2,356	−145	(−489, 78)
Fractures events, Disc.	50	57	−7	(−10, −4)
Number of patient-years in Stage 5	856	1,280	−423	(−617, −208)
Life years	4,288	3,974	315	(142, 516)
Deaths averted/patients alive at end of analysis	739	647	92	(47, 142)
Economic outcomes				
Total costs	$230,666,856	$245,470,802	($14,803,946)	(–$45,224,269, $10,021,090)
Drug costs	$19,525,819	$7,414,227	$12,111,592	
CKD progression costs	$150,967,687	$173,735,113	($22,767,426)	
Fracture costs	$1,422,036	$1,605,690	($183,654)	
CV event costs	$58,485,330	$62,317,219	($3,831,889)	
Total QALYs	2,960	2,620	340	(200, 496)
Incremental cost-effectiveness ratio	—	ERC is dominant	—	
Per patient total costs	$230,667	$245,471	($14,804)	(–$45,224, $10,021)
Per patient QALYs	2.96	2.62	+0.34	(0.20, 0.50)

Abbreviations. CKD, chronic kidney disease; CV, cardiovascular; Disc., discounted; ERC, extended-release calcifediol; QALY, quality-adjusted life year.
*95% CIs estimated from probabilistic sensitivity analysis.

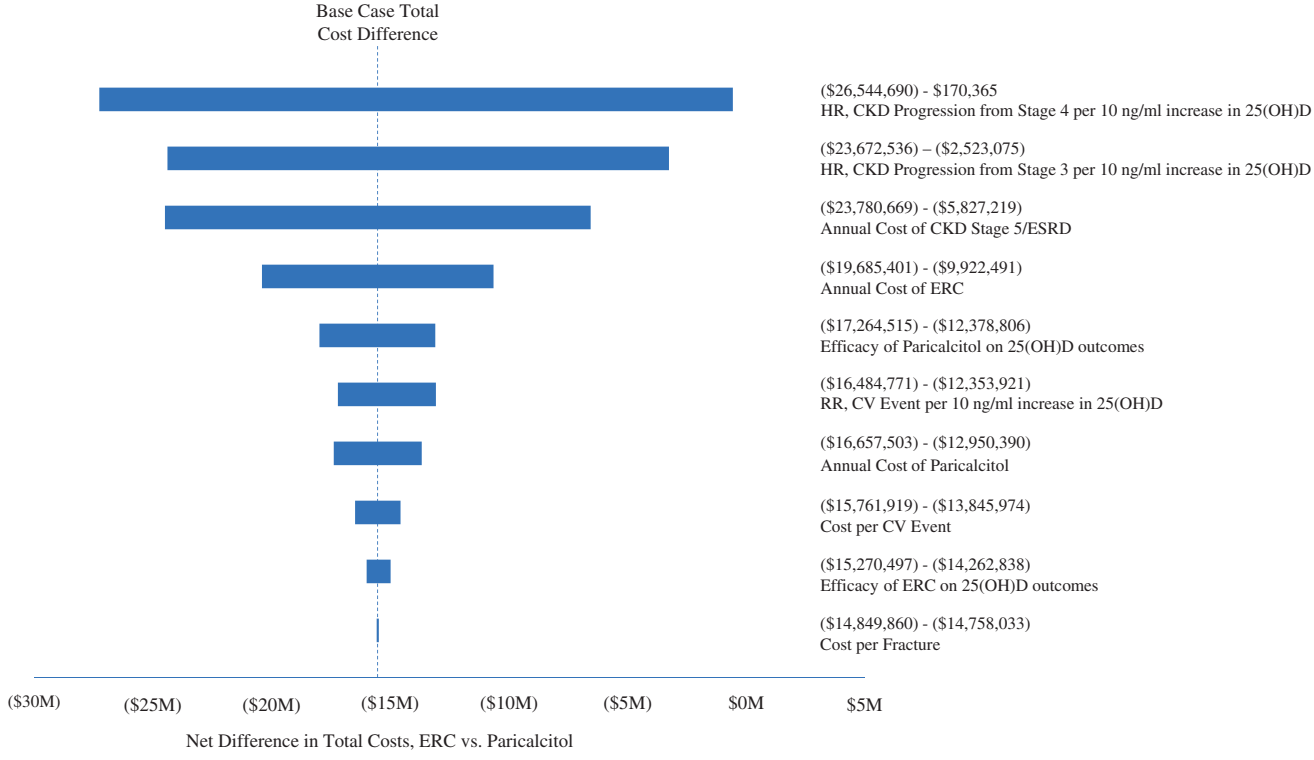

Figure 2. One-way sensitivity analysis results: total cost difference across cohort by parameter tested.
Abbreviations. 25(OH)D, 25-hydroxyvitamin D; CV, cardiovascular; ERC, extended-release calcifediol; ESRD, end-stage renal disease; HR, hazard ratio; RR, risk ratio.

47–142) over the 5-year time horizon. The results are summarized in Table 6.

Cost-effectiveness

The total costs of ERC and paricalcitol over the 5-year time horizon in a 1,000 patient cohort are summarized in Table 6. When compared with paricalcitol, ERC was less costly and more effective for patients with CKD not on dialysis with SHPT and VDI. The overall costs for the ERC cohort were $230.7 M, while the overall costs for the paricalcitol cohort totaled $245.5 M. While the drug cost of ERC was ~$12 M greater than paricalcitol, the reduction in CKD progression costs as a result of ERC's effectiveness resulted in savings of nearly $23 M. Treatment with ERC also resulted in an additional 2,960 QALYs compared to 2,620 QALYs gained with paricalcitol, a difference of 340 QALYs (95% CI = 200–496).

One-way sensitivity analysis

The results were robust to one-way sensitivity analyses. The HR associated with CKD progression from Stage 4 to Stage 5 was the most sensitive input. When sampling the distribution of the CKD progression HR using the bounds of the 95% CI

Table 7. Probabilistic sensitivity analysis results.

	Minimum	Maximum	Mean
CV events averted	473	−1,330	−171
Fractures averted	1	13	7
Stage 5 years averted	−65	891	417
Life years gained	−58	684	316
Deaths averted	−1	177	92

Abbreviation. CV, cardiovascular.
Results over 1,000 simulations.

obtained from the literature, treatment with ERC resulted in costs savings of up to $26.5 M in the best case and a cost increase of $0.2 M in the worst case over a 5-year period. Figure 2 illustrates the results of the sensitivity analyses.

Probabilistic sensitivity analysis

The PSA estimated that 75.7% of simulations identified ERC as the less costly and more effective treatment option compared to paricalcitol. Results for primary clinical outcomes are provided in Table 7.

Discussion

The cost-effectiveness analysis showed that ERC is a cost-effective treatment for patients with CKD stages 3 and 4 with SHPT and VDI when compared with paricalcitol. Treatment with ERC is less costly than paricalcitol, driven primarily by the CV events averted and the reduction in CKD stage 5 years that are offset by superior 25(OH)D and iPTH outcomes. The clinical outcomes of treatment with ERC are more favorable, including fewer CV events, fractures, patient-years in CKD Stage 5, and additional life years gained compared to treatment with paricalcitol. The comparison of ERC to paricalcitol is of particular interest in light of the recent update of the KDIGO clinical practice guidelines which recommend against routine use of vitamin D analogs in patients with CKD stages 3–5 due to an increased risk of hypercalcemia. ERC has been shown to correct VDI and control iPTH without meaningfully perturbing calcium homeostasis.

Modeling involves a variety of assumptions regarding CKD, treatment patterns, and costs. The validity of the assumptions (e.g. adherence rates) have not been assessed in a real-world setting. The model utilizes drug acquisition costs, prevalence, and treatment rates from a claims database or published sources; however, the default values in the model may vary from what is seen in actual practice. Furthermore, patient characteristics, such as tolerability of treatment, comorbidities, and other factors that may potentially impact selection and treatment response, were not included in the model.

To estimate the cost-effectiveness of therapies for SHPT and VDI, the causal relationship between correction of these disease states and a reduced incidence of CV events, fractures, and CKD progression was based on observational associations in the literature. Numerous studies have demonstrated a statistically significant relationship between SHPT and/or VDI and an increased risk of hospitalization and death due to CV disease[39–41], increased risk for bone fractures[42,43], as well as an increased risk for disease progression[30,44,45] in patients with CKD. However, the sufficiency of evidence to support a causal association between laboratory parameters and clinical outcomes, particularly pertaining to vitamin D status and CV disease risk, has been widely debated. In an assessment using Hill's criteria for causality[46], Weyland *et al.*[47] reported that all relevant Hill criteria for a causal association in a biological system were satisfied to indicate that VDI is a risk factor for cardiovascular disease. Previously published cost-effectiveness analyses of vitamin D receptor activators and/or calcimimetics used to treat SHPT in patients with CKD were based on the assumed relationship between modifiable laboratory parameters (e.g. iPTH and 25(OH)D) and CV outcomes[48–50].

In an RCT evaluating the impact of cinacalcet treatment on risk of CV events or CV-related death in dialysis patients with SHPT, the authors reported significant reductions in the cinacalcet group compared to placebo in both the primary composite endpoint of death or the first non-fatal CV event (HR = 0.85; 95% CI = 0.71–0.95; $p = 0.003$) and mortality (HR = 0.83; 95% CI = 0.73–0.96; $p = 0.009$) in a prespecified companion analysis with lag censoring of patient data after 6 months of study drug discontinuation[51]. A meta-analysis of seven RCTs evaluating the effect of active vitamin D analogs on CV outcomes in pre-dialysis CKD reported a reduced incidence in CV events (RR = 0.27; 95% CI = 0.13–0.59) compared to control groups[25]. A more recent meta-analysis of 21 RCTs evaluating treatment with paricalcitol in CKD patients also reported a reduced risk of CV events (RR = 0.55; 95% CI = 0.35–0.87; $p = 0.01$) compared to placebo[52]. While direct evidence of causality from RCTs is limited, these data support the correction of SHPT and/or VDI as a mechanism to reduce the incidence of cardiovascular events.

Because ERC was approved in November 2016, long-term outcomes data are limited to a small number of randomized clinical trials. Approaches that can forecast and estimate outcomes over a longer time horizon may provide broader context for the clinical efficacy as well as the downstream consequences of treatment with ERC. Real-world outcomes are needed to confirm the outputs of the model. Future analyses of ERC are warranted to understand how it compares to other SHPT treatments, but this preliminary analysis indicates that ERC may be cost-effective for patients with CKD Stages 3 and 4 and VDI for the treatment of SHPT.

Conclusions

In this cost-effectiveness model of patients with CKD stages 3 and 4 with SHPT and VDI, ERC was dominant (ERC was less costly and more effective) when compared to paricalcitol. Use of ERC in this patient population could result in cost savings and improved outcomes. The results were robust to one-way and probabilistic sensitivity analyses and were most sensitive to the inputs for CKD progression. Given the assumptions and limitations associated with modeling, real-world evidence is necessary to corroborate the current findings.

Transparency

Declaration of funding

OPKO Health, Inc. funded the model development upon which this manuscript was based, as well as manuscript development. The funder had a role in the study design, collection of data, and the decision to submit the report for publication

Declaration of financial/other interests

Akhtar Ashfaq is an employee of OPKO Health, Inc. Sophie Snyder and Roy Arguello are employees of BluePath Solutions.

A peer reviewer on this manuscript has disclosed that they have received advisory and lecture honoraria as an expert on vitamin D in CKD from both Vifor Fresenius Medical Care Renal Pharma (extended release calcifediol) and AbbVie (paricalcitol). The peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

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Previous presentations

The manuscript is a sub-analysis of a model that was presented as a poster at the National Kidney Foundation (NKF) Clinical Meeting in May 2019.

Data availability

The data to support our model and conclusions can be made partially available upon request. The proprietary modeling code and some of the data are confidential and cannot be made fully available.

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