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Extended-Release Calcifediol: A Data Journey From Phase 3 Studies to Real-World Evidence Highlights the Importance of Early Treatment of Secondary Hyperparathyroidism

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Introduction

- Secondary hyperparathyroidism (SHPT) is characterized by excessive secretion of parathyroid hormone (PTH) and is present in patients with chronic kidney disease (CKD), affecting 40% of individuals with stage 3 CKD and 82% of individuals with stage 4 CKD[1,2]
- In the absence of effective treatment, prolonged and progressive elevations in PTH levels increase the risk of bone disease, fractures, cardiovascular and soft tissue calcification, morbidity and mortality, and may lead to therapeutic resistance[1,3–7]
- The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends that patients with stage 3 or 4 CKD and progressively rising or persistently elevated PTH levels above the upper limit of normal should be tested for vitamin D insufficiency (VDI) and that cases of VDI should be corrected[8]
- However, there is currently no globally accepted standard of care for the management of VDI in non-dialysis CKD patients, and optimal treatment for SHPT in the early stages of CKD remains undefined[9]
- Extended-release calcifediol (ERC) is approved for the treatment of SHPT in patients with stage 3 or 4 CKD and VDI,[10,11] and data that demonstrate the safety and efficacy of ERC in this patient population are now available from both Phase 3 randomized controlled trials (RCTs) and real-world evidence (RWE) studies[12,13]

Objectives

The aims of this analysis were:

- To describe and evaluate whether baseline characteristics and outcomes of patients receiving ERC in RWE settings reflect those reported in RCTs
- To assess whether both datasets could be 'bridged' in a 'continuum' of care in order to optimize the role of ERC in individuals with non-dialysis CKD and SHPT

Methods

- In this descriptive analysis, 25-hydroxyvitamin D (25(OH)D), intact PTH (iPTH), calcium (Ca), phosphorus (P), and estimated glomerular filtration rate (eGFR) of patients randomized to ERC in two identical and concurrent Phase 3 clinical studies were compared with patients treated with ERC in a RWE study
- Studies 3001 (NCT01651000 [N=141]) and 3002 (NCT01704079 [N=144]) were multicenter, randomized, double-blind, 26-week, placebo-controlled studies of ERC in patients with stage 3 or 4 CKD, SHPT, and VDI[12]
- MBD-AWARE was a retrospective analysis of patients with stage 3 or 4 CKD, which reviewed medical records from 15 nephrology clinics in the USA and reported the characteristics of patients who met the study criteria* and were treated with ERC (N=174)[13]

Results

Baseline (BL) characteristics

- The BL characteristics of patients in the Phase 3 clinical trial program were generally consistent with those in the RWE cohort (Table 1)[12,13]
- There was a balanced stratification of patients with stage 3 and stage 4 CKD in the RCTs,[12] whereas in the RWE cohort slightly more patients treated with ERC were in stage 4 vs stage 3 (approximately 53% vs 47%) (Table 1)[13]
- Overall kidney function was similar between the three populations, although patients in the RWE cohort had higher levels of BL iPTH than were seen in the RCTs (Table 1)[12,13]
- When iPTH levels in the RWE cohort were stratified by CKD stage, higher iPTH levels were seen in patients with stage 4 CKD (mean ± standard deviation (SD): 203 ± 109 pg/mL) than in patients with stage 3 CKD (mean ± SD: 156 ± 75 pg/mL)[13]

Results

Table 1. Demographics and disease characteristics of patients treated with ERC in the Phase 3 clinical trials and MBD-AWARE RWE study[12–14]

	RCTs		RWE
	3001 ERC (N=141)	3002 ERC (N=144)	MBD-AWARE ERC (N=174)
PATIENT DEMOGRAPHICS			
Age (years), mean (SD)	65.1 (10.3)	66.8 (10.9)	69.0 (13.2)
Male, n (%)	70 (49.6)	73 (50.7)	84 (48.3)
CKD CHARACTERISTICS			
CKD stage, n (%) 3 4	 71 (50.4) 70 (49.6)	 80 (55.6) 64 (44.4)	 81 (46.6) 93 (53.4)
LABORATORY PARAMETERS			
Plasma iPTH (pg/mL) Mean (SD)	146.8 (56.01)	147.6 (64.21)	181.4 (97.6)
eGFR (mL/min/1.73 m²) Mean (SD)	30.3 (11.1)	30.9 (9.9)	31.1 (14.5)
Serum 25(OH)D (ng/mL) Mean (SD)	20.2 (5.1)	19.7 (5.6)	20.3 (9.2)

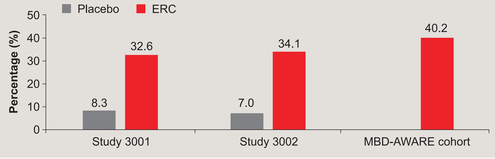
Dose and duration of ERC

- In the RCTs, 74% of subjects were uptitrated to the maximum dose of 60 µg/day after the first 12 weeks,[12] whereas only 1.7% of subjects were uptitrated in the RWE cohort[13]

Effectiveness of ERC

- More than 95% of subjects in the RCTs attained 25(OH)D levels of ≥30 ng/mL, and 33–34% achieved ≥30% reductions in iPTH vs 7–8% in the placebo group[12] (Figure 1)
- Despite the low rates of uptitration in the RWE study, 25(OH)D levels of ≥30 ng/mL were achieved by approximately 70% of subjects, with around 40% achieving a ≥30% reduction in iPTH (Figure 1), consistent with the results seen in the RCTs[13]
- In the RCTs and the RWE study, ERC effectiveness was unaffected by CKD stage[12–14]

Figure 1. Percentage of patients achieving ≥30% reduction in iPTH at Weeks 20–26 of treatment†[12,13]



Safety

- In the RCTs, mean changes in serum Ca levels at the primary efficacy assessment were <3% overall and statistically significant increases occurred in the CKD stage 3 group treated with ERC in study 3001 at the efficacy assessment phase† (EAP) (p<0.005, mean ± SD: 0.2 ± 0.29 mg/dL vs placebo: 0.0 ± 0.27 mg/dL) and in the CKD stage 4 group treated with ERC in study 3002 at Week 12 (p<0.05, mean ± SD: 0.1 ± 0.39 mg/dL vs placebo: -0.1 ± 0.39 mg/dL) and at EAP (p<0.005, mean ± SD: 0.2 ± 0.28 mg/dL vs placebo: 0.0 ± 0.35 mg/dL)
- Significant increases in serum Ca levels were not observed with ERC in the RWE setting, with only 1.8% of patients reporting hypercalcemia[13,14]

Conclusions

- Following on from the results of the Phase 3 clinical studies, the RWE summarized here supports the favorable tolerability and effectiveness of ERC in routine clinical practice[12–15]
- A clinically relevant response was observed with ERC in the real-world study, consistent with the Phase 3 clinical studies, despite higher BL iPTH levels and lower ERC dose
- These data suggest a 'continuum' of clinical evidence of ERC effectiveness for treating SHPT, irrespective of CKD stage
- Initiating ERC early could alleviate the long-term challenges in controlling iPTH within the desired range
- Close safety laboratory monitoring is required as per label recommendations to allow uptitration of ERC

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Disclosures

D Merante, H Schou, I Morin, and M Manu are employees of CSL Vifor.
A Ashfaq, C Bishop, and S Strugnell are employees of OPKO Pharmaceuticals.

*Key inclusion criteria for the study were a diagnosis of CKD stage 3 or 4, as determined by an eGFR ≥15 and <60 mL/min/1.73 m² prior to the index date, and a history of VDI and SHPT.
†In the Phase 3 study, end of assessment period was defined as the last 6 weeks of the 26-week double-blind treatment period. In the real-world study, mean treatment duration was 23.4 weeks.

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