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 stage 3 CKD and 82% of stage 4+ CKD.¹

• In the absence of effective treatment, protracted 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.³

• The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends that patients with stage 3+ CKD and progressively rising iPTH levels who have the upper limit of normal should be tested for vitamin D sufficiency (VDS) and the case of VDS should be corrected.⁴

• 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.⁴

Extended-release calcifediol (ERC) is approved for the treatment of SHPT in patients with stage 3+ CKD and VDI, 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.⁴

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 stage 3+ 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 1001 (NCT01671001; [N=144]) and 3002 (NCT01710419; [N=144]) were multicenter, randomized, double-blind, 26-week, placebo-controlled studies of ERC in patients with stage 3+ CKD, SHPT, and VDI.⁵

• MBD-AWARE was a retrospective analysis of patients with stage 3+ CKD, which reviewed medical records from 15 non-dialysis CKD and SHPT centers (ERCs: N=174) in the US and reported the characteristics of patients who met the study criteria and were treated with ERC (N=91).⁶

Results

Table 1. Demographics and characteristics of patients treated with ERC in the Phase 3 clinical trials and MBD-AWARE RWE study.⁷,⁸

<table>
<thead>
<tr>
<th>CKD CHARACTERISTICS</th>
<th>Phase 3 study</th>
<th>MBD-AWARE RWE study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>70 (49.6)</td>
<td>93 (53.4)</td>
</tr>
<tr>
<td>4</td>
<td>71 (50.4)</td>
<td>81 (46.6)</td>
</tr>
</tbody>
</table>

Table 2. Laboratory parameters of patients treated with ERC in the Phase 3 clinical trials and MBD-AWARE RWE study.⁷,⁸

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Phase 3 study</th>
<th>MBD-AWARE RWE study</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (ng/mL)</td>
<td>348.5 (45.0)</td>
<td>330.5 (55.0)</td>
</tr>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>30.3 (11.1)</td>
<td>31.1 (11.5)</td>
</tr>
</tbody>
</table>

Table 3. Patient demographics of patients treated with ERC in the Phase 3 clinical trials and MBD-AWARE RWE study.⁷,⁸

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Phase 3 study</th>
<th>MBD-AWARE RWE study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>35.4 (11.1)</td>
<td>35.1 (11.7)</td>
</tr>
</tbody>
</table>

Baseline (BL) characteristics of patients in the Phase 3 clinical trial were generally consistent with those in the RWE cohort (Table 1).⁷,⁸

• There was a balanced stratification of patients between stage 3 and stage 4 CKD in the RWE cohort although more patients treated with ERC were in stage 4+ CKD (Table 1)⁷,⁸

• Overall, the characteristics were similar between the three populations, although patients in the RWE cohort had higher levels of iPTH than seen in the RCTs (Table 1)⁷,⁸

• When iPTH levels in the RWE cohort were stratified by CKD stage, higher iPTH levels were seen in patients with stage 4+ CKD compared with patients treated with ERC in a RWE study (approximately 53% vs 47%) (Table 1)³,⁴

Effectiveness of ERC

• In the RCTs, 74% of subjects were uptitrated to the maximum dose of 60 μg/day after the first 12 weeks, whereas only 1.7% of subjects were uptitrated in the RWE cohort.⁷,⁸

• Despite the low rates of uptitration in the RWE study, 25(OH)D levels of ≥30 ng/mL were achieved by approximately 70% of patients in the RWE setting, with only 1.4% reporting hypercalcemia.⁷,⁸

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 3002 (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 Weeks 12 to 18, mean ± SD: 0.1 ± 0.29 mg/dL vs placebo: 0.1 ± 0.30 mg/dL and at EAP at 12 weeks; 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, only with 1.8% of patients reporting hypercalcemia.⁷,⁸

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.⁷,⁸

• A clinically relevant response was observed with ERC in the real-world setting, compared with the Phase 3 clinical studies, despite higher BL iPTH levels and lower ERC dose.

• These data support 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.

References


Figure 1. Percentage of patients achieving ≥30% reduction in iPTH at Weeks 20–26 of treatment.⁷,⁸

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Disclosures

D Merante, I Schou, M Morin and M Manu are employees of CSL Vifor.

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