Head-to-head comparison of the new calcimimetic agent evocalcet with cinacalcet in Japanese hemodialysis patients with secondary hyperparathyroidism

OPEN

Masafumi Fukagawa[1], Ryutaro Shimazaki[2] and Tadao Akizawa[3]; and the Evocalcet study group

[1]Division of Nephrology, Endocrinology, and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan; [2]R&D Division, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; and [3]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Secondary hyperparathyroidism (SHPT) leads to cardiovascular calcification, which affects survival and quality of life in patients with chronic kidney disease. Cinacalcet is used to control SHPT, but it may induce gastrointestinal symptoms, resulting in lower adherence and insufficient dosages. Therefore, a need exists to develop new calcimimetics that cause fewer gastrointestinal symptoms. Here we conducted a phase 3, randomized, double-blind, double-dummy trial for a head-to-head comparison of the efficacy and safety of evocalcet, a new oral calcimimetic, to the established cinacalcet. Japanese patients with SHPT on hemodialysis were randomized to receive evocalcet or cinacalcet (317 patients each) for 30 weeks. The primary efficacy endpoint was non-inferiority of evocalcet to cinacalcet in the proportion of patients achieving a mean intact parathyroid hormone level of 60 to 240 pg/mL from week 28 to 30 (non-inferiority margin, −15%, per protocol set analyses). In the evocalcet and cinacalcet groups, 72.7% and 76.7%, respectively, achieved the target intact parathyroid hormone level (between-group difference: −4.0% [95% confidence interval −11.4%, 3.5%], for non-inferiority). The incidence of gastrointestinal-related adverse events was 18.6% and 32.8%, respectively (between-group difference: −14.2% [−20.9%, −7.5%], significant for superiority). Thus, the non-inferiority of evocalcet to cinacalcet in suppressing intact parathyroid hormone with fewer gastrointestinal-related adverse events was demonstrated. Hence, evocalcet may be a favorable alternative to existing calcimimetics for management of SHPT.

Kidney International (2018) ■, ■–■; https://doi.org/10.1016/j.kint.2018.05.013

KEYWORDS: cinacalcet; evocalcet; gastrointestinal; Japan; randomized controlled trial; secondary hyperparathyroidism

Correspondence: *Masafumi Fukagawa, Division of Nephrology, Endocrinology, and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. E-mail: fukagawa@tokai-u.jp*

Received 30 January 2018; revised 19 April 2018; accepted 10 May 2018

Secondary hyperparathyroidism (SHPT) is one of the most common complications of chronic kidney disease–mineral and bone disorder.[1,2] Excessive parathyroid hormone (PTH) secretion often causes cardiovascular calcification, which substantially impairs the survival and quality of life of these patients.[1] Accordingly, in chronic kidney disease patients it is important to manage intact PTH (iPTH) levels as well as those of serum calcium and phosphorus.[3]

For the prevention and management of SHPT, oral phosphate binders and oral or i.v. vitamin D receptor activators have long been used. However, the development of hypercalcemia and hyperphosphatemia was one of the problems associated with vitamin D receptor activator therapy.[1]

Cinacalcet hydrochloride is an oral calcimimetic agent that acts allosterically on the calcium-sensing receptor on parathyroid cells to suppress PTH secretion. In contrast to vitamin D receptor activators, cinacalcet decreases serum levels of calcium and phosphorus. Thus, cinacalcet therapy has been demonstrated to significantly increase the achievement rate of target levels of serum iPTH, calcium, and phosphorus[4–6] and has been suggested to decrease the risk of vascular calcification and mortality.[7,8]

Despite such favorable effects, gastrointestinal (GI) symptoms and drug interactions (cytochrome P450 [CYP] 2D6 inhibition and CYP3A4-mediated metabolism) remain important concerns in cinacalcet treatment.[9,10] GI-related adverse events (AEs) especially are critically responsible for low adherence and insufficient dosage.[11]

Etelcalcetide is a new calcimimetic agent for i.v. use developed to improve adherence. However, there remains an unmet need to develop a calcimimetic agent that causes fewer GI symptoms than cinacalcet and etelcalcetide.[12]

Evocalcet is another new calcimimetic agent for oral use developed to address the issues reported with cinacalcet use. In addition to suppression of PTH, this agent was selected for further investigation because of its favorable profile by evaluating the effect on gastric emptying in rats and the interaction

with CYPs in human liver microsomes.[13] The present phase 3 clinical trial was conducted with a double-dummy, double-blind design to investigate the efficacy (noninferiority) and safety of evocalcet, with cinacalcet as the comparator.

RESULTS

A total of 639 patients were enrolled (320 randomized to receive evocalcet and 319 to receive cinacalcet) from October 2015 to April 2016, with the end-of-participant follow-up in November 2016. The disposition of patients is shown in Figure 1. Five patients discontinued the study before initiating treatment; thus, 634 patients received treatment with evocalcet or cinacalcet (n = 317, each). Of these patients, 526 patients (evocalcet group, 256; cinacalcet group, 270) completed the study. A total of 519 patients (evocalcet group, 253; cinacalcet group, 266) were included in the per-protocol set, 623 patients (evocalcet group, 313; cinacalcet group, 310) were included in the full analysis set, and 634 patients (evocalcet group, 317; cinacalcet group, 317) were included in the safety analysis set.

Patient baseline demographic and clinical characteristics are summarized in Table 1. More than 60% of patients in both groups had previously received cinacalcet treatment. More than 20% of patients in both groups had baseline iPTH ≥ 500 pg/ml. Overall, patient characteristics were well balanced between the 2 treatment groups. In the per-protocol set, 153 and 175 patients used cinacalcet before treatment initiation in the evocalcet and cinacalcet groups, respectively, and the mean (SD) duration of cinacalcet treatment before wash-out prior to treatment initiation was comparable: 3.45 (2.55) years and 3.97 (2.62) years. During the evaluation period (28–30 weeks), the median average daily dose (SD) was 3.5 mg (2.4 mg) for evocalcet and 49.20 mg (30.09 mg) for cinacalcet.

Efficacy

Among 519 patients in the per-protocol set (primary analysis set), the number (%) (95% confidence interval [CI]) of patients who achieved the target iPTH level (primary endpoint) was 184 (72.7%) (66.8%, 78.1%) and 204 (76.7%) (71.1%, 81.6%) in the evocalcet and cinacalcet groups, respectively. The difference in the achievement rates between the groups was −4.0% (95% CI −11.4%, 3.5%, *P* for noninferiority, $P = 0.002$). Because the lower limit of the 2-sided 95% CI for the difference was −11.4%, which exceeded the noninferiority margin of −15%, the noninferiority of evocalcet to cinacalcet was confirmed. In the full analysis set (secondary analysis set), the nonresponder imputation (assumes participants with missing outcomes are nonresponders) results were not consistent with those of the per-protocol set; however, the results of last observation carried forward and multiple

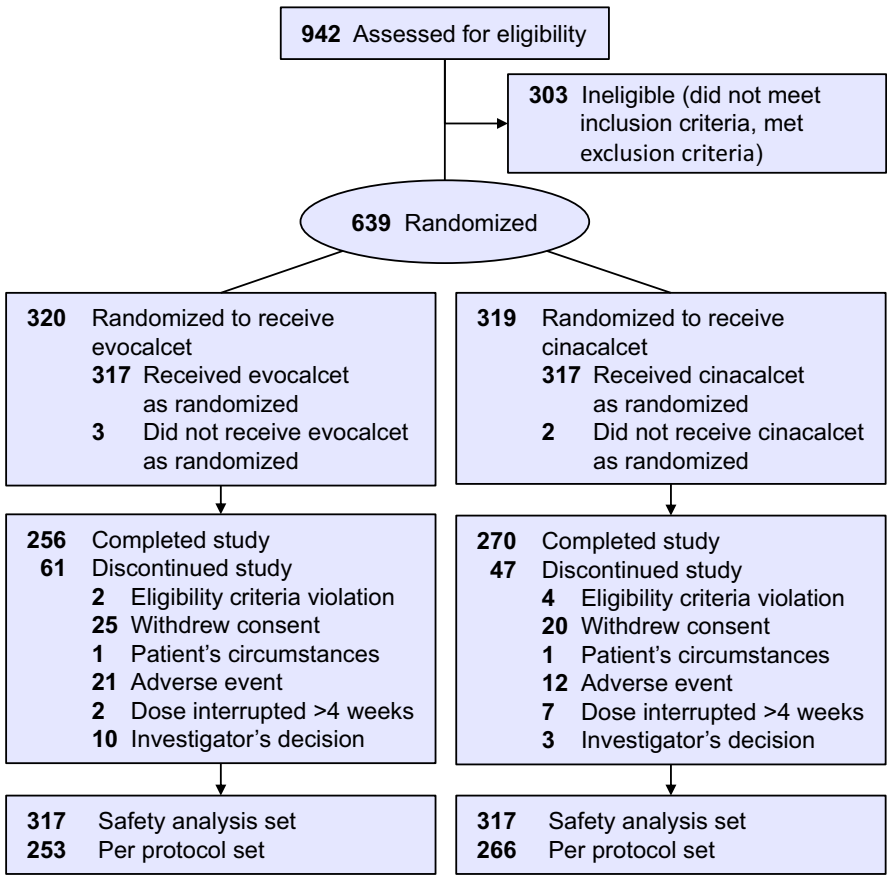

Figure 1 | Patient disposition.