In end stage renal failure, elevation of serum phosphorus, decrease of serum vitamin D and decrease of serum calcium accelerate parathyroid hormone (PTH) secretions and promote proliferation of parathyroid cells, and finally cause secondary hyperparathyroidism (SHPT). In SHPT, extremely high PTH induces high-turnover bone disease and accelerates elution of Ca and P from bone which is associated with vascular calcification, fracture and increased risk of cardiovascular diseases and mortality.

The secretion of PTH from the parathyroid gland is controlled through the calcium receptor (CaR) which senses slight changes of serum Ca concentration. A compound that acts on CaR as mimic the action of Ca is called calcimimetic.

Cinacalcet, the first launched calcimimetic drug for SHPT patients adequately controlled serum PTH and Ca levels and drastically reduced parathyroidectomy (PTx). Additionally, cinacalcet also reduced the progression of cardiovascular calcification and the risk of mortality in hemodialysis patients with SHPT.

However, cinacalcet caused GI side effects such as nausea and vomiting, making difficult either continuous use or increase dosage. Such GI intolerability thereby limited the dosage of cinacalcet, resulting in poor compliance or discontinuation.

Evocalcet (MT-4580/KHK7580) was a novel oral calcimimetic compound developed for patients with SHPT and was expected to improve upon several issues associated with cinacalcet. In order to characterize evocalcet, we performed in vitro and in vivo studies.

In HEK293 cells expressing the human CaR, evocalcet shifted the extracellular Ca$^{2+}$ concentration response curve to the lower concentration side in the dose-dependent manner, suggesting that this agent had the characteristics of an allosteric modulator of CaR. Evocalcet suppressed the serum PTH and calcium levels in both normal and 5/6 Nx rats as well as cinacalcet, but the effective dose was extremely lower than cinacalcet. The bioavailability of evocalcet in rats was more than 80% although that of cinacalacet in rats is approximately 1-2%. It was suggested that, because of almost same affinity in two compounds, such a higher bioavailability contributed to dose reduction. Evocalcet did not delay the gastric emptying rate at a minimum effective dose to observe a significant PTH reduction. Evocalcet did not cause emesis in common marmosets and miniature pigs in comparison to cinacalcet. This difference might be because evocalcet needed a less dosage than cinacalcet which meant the subject could avoid to expose to the excess amount of drugs in the GI tract.

A phase 3 clinical trial about evocalcet was conducted with a double-dummy, double-blind design to investigate its efficacy and safety using cinacalcet as a control drug. More than 300 patients with SHPT were enrolled to the trial and received treatment with either evocalcet or cinacalcet in each group. Among 519 patients in the per protocol set, the number of patients who achieved the target iPTH level (60–240 pg/mL) was 184 (72.7%) and 204 (76.7%) in the evocalcet and cinacalcet groups, respectively. The number of patients who achieved a ≥30% decrease in iPTH level from baseline, and the mean percent change of the iPTH level was comparable between evocalcet and cinacalcet groups. Serum calcium, serum phosphorus and intact fibroblast growth factor 23 (FGF23) were decreased by evocalcet as well as cinacalcet. The mean levels of the bone turnover markers, bone-specific alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP-5b), and total N-terminal propeptide of type 1 procollagen (P1NP), decreased over time demonstrating a similar trend in both groups. The overall incidence of GI-related AEs (nausea, vomiting, abdominal discomfort, decreased appetite and abdominal distension) was lower in evocalcet group than cinacalcet group. It was 18.6 % and 32.8 % in evocalcet and cinacalcet groups, respectively. To sum
up, in this head-to-head comparison study, evocalcet was validated to be non-inferior to cinacalcet to suppress iPTH levels in hemodialysis patients with the lower incidence of GI-related AEs. Thus, our results suggest that evocalcet could be a potent alternative to cinacalcet for the management of SHPT with less GI-related AEs.