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BIOBUSINESS BRIEFS

DEAL WATCH

Amgen builds secondary hyperparathyroidism pipeline

Amgen has announced it will buy Kai Pharmaceuticals for US$315 million. Kai's lead candidate, KAI-4169, is set to begin Phase III trials for treating secondary hyperparathyroidism (SHPT) in dialysis patients with chronic kidney disease (CKD), and so could join Amgen's cinacalcet (Sensipar/Mimpara) as a calcimimetic for this indication.

SHPT is a progressive condition seen in nearly all patients with CKD, in which the parathyroid glands produce excessive amounts of parathyroid hormone (PTH), explains Geoffrey Block, Director of Clinical Research at Denver Nephrology, Colorado, USA. "The precise aetiology of SHPT is multifactorial; it involves decreased 1,25-dihydroxyvitamin D_3 [the hormonally active form of vitamin D], decreased serum calcium, increased serum phosphate and increased FGF23 [fibroblast growth factor 23]," he adds.

According to Albert Fournier, Chief of the Department of Nephrology-Internal Medicine Intensive Care, CHU Sud, France, the high prevalence of SHPT in dialysis patients is because of the lack of prevention, mainly based on maintaining adequate vitamin D repletion (25-OH vitamin D levels between 30 ng per ml and 50 ng per ml). "This is rarely implemented, and so ultimately the depletion in vitamin D leads to low 1,25-dihydroxyvitamin D and hypocalcaemia, which trigger PTH synthesis and release," he adds. If left untreated, "SHPT increases cortical bone resorption and therefore the risk of long-bone fracture, and the increased bone resorption increases the calcium•phosphate product, which is a major risk factor for artery and vascular calcification, and therefore of possible cardiovascular events," says Fournier.

The number of factors involved in SHPT has led to various approaches being pursued to try and redress the imbalances, including the use of phosphate-binding agents and vitamin D analogues. However, these agents have various side effects and limited efficacy.

The discovery of calcium-sensing receptors (CaSRs) on the parathyroid gland in 1993 and elucidation of their role as the main regulators of PTH secretion prompted a new direction of research that culminated in the launch in 2004 of the first-in-class calcimimetic cinacalcet, which is a positive allosteric modulator of the CaSR. "One advantage of using calcimimetics over active vitamin D compounds (in isolation) is that calcimimetics reduce levels of serum calcium and phosphate, as well as FGF23, whereas active vitamin D analogues have the opposite effect," says Block.

Although cinacalcet is effective, it is associated with dose-limiting gastrointestinal side effects that can occasionally lead to treatment discontinuation. KAI-4169 is a peptidic direct agonist of the CaSR that is administered intravenously three times a week, compared with once-a-day oral dosing for cinacalcet. In studies so far, KAI-4169 has not shown gastrointestinal side effects and its intravenous administration allows it to be given with dialysis sessions. "If the intravenous administration [of KAI-4169] is better tolerated, treatment observance will be improved and therefore the control of SHPT and vascular calcifications," says Fournier.

Overall, it is likely, however, that a combination of drugs is needed to effectively control SHPT, as Fournier explains: "Use of native vitamin D or lower doses of potentiated vitamin D together with CaSR modulators could help to control moderate to severe hyperparathyroidism with lower plasma phosphate and calcium concentrations, resulting in attenuation of vascular and cardiac valve calcification, as suggested by the ADVANCE study (*Nephrol. Dial. Transplant.* **26**, 1327–1339; 2011)."

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