Evaluate Vantage

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Therapeutic focus - Amgen buys novel kidney disease treatment as bundling bites

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Amgen's $315m buyout of Kai Pharmaceuticals this week, to acquire the private Japanese group's secondary hyperparathyroidism drug KAI-4169, is a strategic move to defend an important part of its revenue stream. The California group has snapped up the most-advanced unpartnered novel candidate in a pipeline of assets looking to improve upon current treatment strategies, primarily generic vitamin D analogues, which are used to reduce levels of parathyroid hormone in patients with late-stage chronic kidney disease (CKD).

As owner of the best-selling secondary hyperparathyroidism drug Sensipar as well as the chunky anti-anaemic franchise of Epogen and Aranesp, the California company would do well to protect and grow its domain in treating CKD patients. But as a review of the pipeline shows, Kai is not the only company trying novel approaches for the condition (see tables). With treatments for CKD coming under increasingly tight pricing pressure under US government reimbursement rules, new drugs will need to demonstrate a clear improvement in value, as well as clinical benefit.

Complication

Kidney disease is the most common cause of secondary hyperparathyroidism, which itself is a result of chronically low levels of calcium and inhibition of the body's ability to remove phosphate. The parathyroid gland produces excessive amounts of the eponymous hormone parathyroid in response to the nutrient imbalances; the hormone imbalance leads to accelerated bone resorption as the body seeks to normalise calcium levels, which in turn leads to bone deformities, swollen joints and fractures. It can also lead to vascular calcification and cardiovascular events.

In the US there are approximately 600,000 patients with Stage 5 CKD and eight million patients with Stage 3/4 disease. Most patients with Stage 5 CKD or end-stage renal disease on dialysis have elevated parathyroid hormone and secondary hyperparathyroidism of varying severity.

Medication options to reduce hormone levels to a range that supports normal bone turnover and minimises soft tissue calcification include phosphate binders, vitamin D and its analogues, and calcimimetics that mimic the effect of calcium on calcium receptors. Having been around for a lot longer, globally the vitamin D analogues are used most widely, including what remains the top selling branded drug in that class, Abbott Laboratories' Zemplar, which is forecast to bring in around $300m annually for the Illinois group (see table below).

A newer oral agent, Amgen's Sensipar is a calcimimetic that binds with calcium-sensing receptors on the parathyroid cell surface. It increases the extracellular calcium sensitivity of the receptor to lower circulating parathyroid hormone levels.

Main branded hyperparathyroid products (ex Asia)					**Sales ($m)**				
Product	**Company**	**Pharmacological Class**	**Route of admin**	**Patent Expiry**	**2010**	**2012**	**2014**	**2016**	**201**
Sensipar	Amgen	Calcimimetic	oral	08/03/2018	714	896	876	767	686
Zemplar	Abbott Laboratories	Vitamin D analogue	injection	24/06/2014	551	311	279	302	325
Hectorol	Sanofi	Vitamin D2 analogue	injection/oral	11/02/2014	190	185	199	212	225
				Total	*1,455*	*1,392*	*1,354*	*1,281*	*1,23*

Proving value

Changes in the US reimbursement scheme for CKD – patients with kidney failure are covered under the federal Medicare programme even if they do not meet age criteria – may begin putting Sensipar under pressure in 2014. That year, oral drugs without an IV equivalent will begin to be covered by a bundled payment system that went into effect for other aspects of renal dialysis care in 2011. The decline in Zemplar sales after 2010 reflects the impact of this bundling in the US.

The practical effect of the bundling scheme will be that dialysis centres will begin negotiating lower prices with drugmakers. Thus, Amgen is trying to demonstrate Sensipar has even greater value by promoting its positive effects on cardiovascular outcomes.

The Evolve phase III study is testing whether Sensipar treatment reduces the risk of cardiovascular events in dialysis patients with secondary hyperparathyroidism. The data is expected mid 2012, according to Jefferies. Post hoc analysis showed a 19% reduction in mortality and 37% reduction in cardiovascular hospitalisation. The analysts note that if overall results are positive, Sensipar's use in dialysis could increase by about 25%.

Likewise, Abbott and Sanofi are engaged in a similar effort with their vitamin D analogues Zemplar and Hectorol in demonstrating cardiovascular benefits. Phase IV trials could report later in 2012.

In the pipeline

Despite the seeming dominance of well established large players, a number of smaller companies are researching ways to improve the treatment of secondary hyperparathyroidism. Amgen's move this week suggests even they see room for improvement.

Like Sensipar KAI-4169 is a calcimimetic, although the product is a peptide with intravenous rather than oral administration. It is ready to enter phase III trials; as part of the buyout Amgen provided a loan to the company to keep preparations on track. Previously, Ono Pharmaceuticals purchased Japanese rights for $13m upfront, developmental and sales milestones and royalties.

At the end of last year Kai released the results of its first phase II study in end stage renal disease patients. The drug was given three times weekly during hemodialysis for up to four weeks. It reduced levels of parathyroid hormone by 33% and 49% from baseline in the 5mg and 10mg dose groups, respectively, in the same ball park as Sensipar's effectiveness. However gastrointestinal adverse events, a fairly big side effect of the Amgen pill, were similar to placebo.

Mark Schoenebaum, an analyst with ISI Group, noted that intravenous dosing would allow patients to receive KAI-4169 in tandem with their dialysis, reducing pill burden and improving patient compliance. With Sensipar going off patent in 2018, it seems Amgen sees the product as a possible line extension.

Others in development

Canadian company Cytochroma is also active in the space, with three compounds in development. The most promising is CTA018 (MT-2832), which Mitsubishi Tanabe in-licensed in the US and Asia in a deal that could be worth up to $105m to the privately held company. CTA018 is a vitamin D analogue injection that not only activates the vitamin D signalling pathway but it also blocks CYP24, an enzyme involved in vitamin D catabolism (see table).

Researchers believe that renal impairment causes CYP24 levels to build in the kidney, leading to vitamin D insufficiency. Treatment resistance can occur with current vitamin D hormone replacement therapies due to induced CYP24. This suggests that CYP24 levels need to be managed in CKD patients to optimise treatment with vitamin D analogues, Cytochroma believes.

In a phase I study CTA018 was well tolerated and produced clinically meaningful improvements in secondary hyperthyroidism after less than two weeks of dosing. According to clinicaltrials.gov a phase II trial in stage 5 patients completed in 2010, however no results have yet been posted.

A second drug, CTAP101 capsules, are currently in phase II/III. These are to treat patients with Stage 3/4 CKD with secondary hyperthyroidism and vitamin D insufficiency. The study completed at the end of 2011 and the results will be released at a medical conference later this year, the company says. The vitamin D analogue previously generated encouraging phase I/II data.

Lastly the company have a vitamin D analogue injection, CTAP201, in phase I. CTAP201 is the active metabolite of doxercalciferol, the active ingredient in Sanofi's Hectoral. A phase I trial comparing CTAP201 to doxercalciferol injection in haemodialysis patients concluded that CTAP201 was approximately twice as effective in raising vitamin D hormone levels.

Secondary hyperparathyroidism pipeline					
Status	**Product**	**Pharmacological Class**	**Company**	**Routes of Admin.**	**Trial ID**
Phase III	CTAP101	Vitamin D analogue	Cytochroma	Oral	NCT01219855
Phase II	MT-2832/CTA018	CYP24 inhibitor & vitamin D analogue	Mitsubishi Tanabe Pharma/Cytochroma	Injection	NCT00742716
	KAI-4169	Calcimimetic	KAI Pharmaceuticals/Amgen (Ono pharmaceuticals in Japan)	Injection	NCT01254565 NCT01414114
Phase I	ASP7991	Anti-parathyroid hormone MAb	Astellas Pharma	Oral	-
	CTAP201	Vitamin D analogue	Cytochroma	Injection	NCT00792857
	LEO 27847	Renal agent	LEO Pharma	Oral	NCT01167309
	Oral inecalcitol	Vitamin D analogue	Hybrigenics	Oral	-
Pre-clinical	KAI-4169 Transdermal	Calcimimetic	KAI Pharmaceuticals/Amgen	Transdermal	-

In phase I

Like Sensipar, Astellas' ASP7991 is also a calcimimetic compound entering phase I. In preclinical studies the compound was compared to Sensipar in terms of its ability to increase intracellular calcium, effect on parathyroid hormone levels levels and ability to inhibit CYP2D6, a drug metabolising enzyme.

In vitro ASP-7991 displayed potent receptor enhancing activity. It showed sufficient parathyroid hormone decreasing effect in vivo and minimum CYP2D6 inhibition. Further studies in adenine-induced secondary hyperparathyroidism in rats showed that ASP-7991 inhibited the increase of parathyroid hormone levels compared to Sensipar, which did not show an effect. Aortic calcification was not detected in rats treated with ASP-7991.

LEO Pharma's compound LEO 27847 completed its phase I trial at the end of last year according to clinicaltrials.gov, the results of which have not yet been published. However, according to the company's 2010 annual report the compound will be sold off, but the status of this is not known.

Hybrigenics' inecalcitol is a derivate of the vitamin D analogue calcitriol, the active ingredient in Abbott's Calcijex, the forerunner to Zemplar. The drug is said to be optimised to have a much less effect on calcemia, and is around 100 times less hypercalcemic than calcitriol in rats.

The drug is currently in phase II in prostate cancer and the company are looking at its use in hyperparathyroidism with the option to license the compound out for this indication.

The question for all of the new drugs will be how well they improve upon existing therapies – expensive drugs showing only incremental gains will probably not be commercially successful in a space where the dialysis centres purchasing them have limited flexibility under new payment practices. If the activity of companies marketing approved drugs is any indication, R&D candidates will not only need to show that they normalise hormone levels but that they also prevent complications.