Evaluate Vantage

September 06, 2011

Roche signs first Alzheimer's deal of the year as crucial progress awaited

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The licensing deal announced today between Roche and Evotec is the first such transaction struck in Alzheimer's disease so far this year – a flicker of partnering activity for a field of drug development that has famously struggled to make much headway in the last couple of years.

Like most of the products that have been partnered in this space recently Evotec's compound is very early stage, having only completed phase I studies (see table). Next year is going to be hugely important for Alzheimer's research with pivotal data due from two of the most advanced projects in the field; clinical progress will be required before bigger and later stage deals become more common.

Free radicals

Roche has paid $10m upfront for worldwide rights to EVT 302, a MAO-B inhibitor that the Swiss pharma giant will take into phase II next year. Double digit royalties on sales and further payments of up to $820m are pending on success.

The drug inhibits monoamine oxidase type B, an enzyme that breaks down dopamine in the brain and contributes to the production of free radicals. Free radicals are known to cause oxidative stress which are thought to contribute to the development of Alzheimer's disease, thus inhibiting MAO-B may treat the symptoms of the disease.

On a conference call today Werner Lanthaler, Evotec chief executive, said they do not believe the drug will be disease modifying. "What we will be going for is slowing down the progression of Alzheimer's symptoms," he said.

Safety has derailed a number of MAO products in the past, but EVT 302 has so far managed to avoid one of the biggest drawbacks in using the this approach, that of tyramine sensitivity, Evotec says.

Foods such as aged cheeses, cured meats, tofu and draught beer all contain high levels of tyramine, which is usually broken down by MAO; inhibiting this process causes blood pressure to rise and has in the past led to fatal hypertension. Mr Lanthaler said that the toxicity profile for the drug had been "as clean as it gets" and added there had been no evidence of drug-food interactions in the years that the drug had been in the clinic.

Worth pursuing

Still, the development of MAO-B inhibitors for Alzheimer's has been somewhat chequered, although the agents are a proven approach to treat Parkinson's disease, with Azilect and Zelapar on the market – Azilect sales reached $318m in 2010.

Indeed Roche had developed the most advanced MAO-B inhibitor so far, lazabemide, which generated decent efficacy data in a phase III trial but was ditched by the Swiss group back in 1999 due to concerns over renal safety. Teva had some success with another MAO-B candidate, ladostigil (TV-3326), but scrapped a phase IIa trial in 2007. Private Israeli company Avraham Pharmaceuticals now holds rights to the drug and is currently conducting a phase II trial.

Roche clearly considers it a mechanism worth pursuing, although the company is certainly hedging its bets with a broad Alzheimer's research pipeline. With the licensing of EVT 302, it has seven active pipeline projects in the disease, most advanced of which are two beta amyloid antibodies, similar to Elan's bapineuzumab.

Crenezumab was licensed by Genentech from AC Immune in 2006, while gantenerumab is an in-house product. Trials of both candidates were initiated recently, with results not expected until 2014 or 2015.

Roche's decision to exercise its option on Evotec's compound could offer encouragement to BioTie Therapies, currently developing a couple of 5-HT6 antagonist candidates in phase I over which Roche still retains opt-in rights; rights that could be triggered after completion of these trials.

Roche's Alzheimer's Disease Pipeline Candidates			
Status	**Product**	**Pharmacological Class**	**Originator**
Phase II	Crenezumab (RG7412)	Anti-beta amyloid MAb	AC Immune
	Gantenerumab (RG1450)	Anti-beta amyloid MAb	Roche
Phase I	SYN-114 (Roche holds option rights from BioTie Therapies)	5-HT6 (serotonin) antagonist	Roche
	SYN-120 (Roche holds option rights from BioTie Therapies)	5-HT6 (serotonin) antagonist	Roche
	RG1662	GABA A agonist	Roche
	EVT 302	MAOB inhibitor	Roche
Pre-clinical	Anti-BACE-1 Antibody	Anti-beta-secretase-1 Antibody	Roche
Research project	Neurodegenerative Disease Project	Alzheimer's disease agent	Roche/Siena Biotech
	ReS19-T	Tau aggregation inhibitor	reMYND

The table below shows that deal activity has ground to a halt this year, and it is certainly true that most Alzheimer's research remains very early stage. Exactly what happens to trigger the disease and what causes the fatal degeneration is still unknown and multiple mechanisms of action are being tested.

Most are testing the amyloid-beta hypothesis – that the accumulation of A-beta plaques causes the degeneration - although tau tangles, RAGE modulators and gamma and beta secretase inhibitors are also being trialled, as well as several agents targeting neurotransmitters, like EVT 302, in an attempt to improve the cognition of patients (*Therapeutic focus - What are plan B options if A-beta Alzheimer's hypothesis is void?, August 19, 2010*).

Progress in any area will certainly trigger a scramble for assets given the huge commercial opportunity Alzheimer's represents. However, few are hopeful of real breakthroughs anytime soon – only this week Moncef Slaoui, GlaxoSmithKline's head of R&D, called for greater co-operation between companies and scientists to get a better grasp on this poorly understood disease, the *Financial Times* reported.

Arguably the biggest events on the horizon for the field are the release of phase III data from bapineuzumab, in which Elan, Pfizer and Johnson & Johnson all have a vested interest, and Eli Lilly's solanezumab - both anti-beta amyloid antibodies designed to block the build up of what are assumed to be damaging plaques in the brain. Results should emerge towards the back end of next year and unfortunately few are anticipating success from what are considered the first test of this approach – many believe more effective antibodies are following behind.

However, the studies will provide important insight into whether Alzheimer's research has been going in the right direction, and whether sorely needed disease modifying agents might be any closer to the market.

	Alzheimer's Product Deal Count				
Status on Deal	**2011 (YTD)**	**2010**	**2009**	**2008**	**2007**
Marketed	-	-	1	-	1
Filed	-	3	3	-	-
Phase III	-	-	3	3	-
Phase II	-	1	3	1	-
Phase I	1	1	2	4	2
Pre-clinical	-	5	4	6	3
Research project	-	15	5	2	9
Total Product Deals	**1**	**25**	**21**	**16**	**15**
Disclosed Upfront Fees ($m)	**10**	**289**	**542**	**455**	**-**
Disclosed Total Deal Values ($m)	**830**	**612**	**1,627**	**2,340**	**671**