Evaluate Vantage

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Should Neurocrine get stressed over CRF1 failure?

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The failure of Neurocrine Biosciences' corticotropin-releasing factor-1 (CRF1) receptor antagonist, GSK561679 (verucerfont), to show any benefit in treating depression represents the latest failure in what has so far been a largely fruitless area of research, certainly in terms of generating approvable products.

Even Neurocrine's chief executive, Kevin Gorman, admitted earlier this week that CRF1 remains a difficult drug target in depression and he should know: the San Diego company has been working on this class for more than 15 years with a series of partners and none of its compounds have made it into phase III trials. It now seems likely that GlaxoSmithKline, Neurocrine's partner on GSK561679 and two other CRF1 candidates, will walk away from the field. This would leave only one candidate remaining in the clinic, SSR 125543, under development by Sanofi-Aventis, with phase II results due in March 2011 and one analyst predicting sales of $125m by 2015 (see table below).

Underlying rationale

The brain chemical CRF is believed to be a central mediator of the body's stress responses, hence the underlying rationale for CRF antagonists as treatments for stress-induced disorders.

CRF is overproduced in clinically-depressed patients and may be dysregulated in people with anxiety disorder. In fact, endocrine, behavioural and immune responses to stress appear to be modulated by CRF. As such, abnormalities in mood, digestion, and immunity are thought to be brought on by stress via this pathway.

Pre-clinical studies of CRF antagonism have suggested that blocking this pathway may reverse the effects of stress-related psychiatric disorders, such as depression. There is also the theory that CRF receptors are responsible for stress-induced changes in colonic motility, hence the rationale for using the antagonists as irritable bowel disease therapies.

Expanding the market

In its last annual report, Neurocrine said it believed that the novelty and specificity of the CRF mechanism of action represented an opportunity to improve on the widely used SSRIs, like Eli Lilly's Prozac, and expand the market. At the same time CRFs would offer better efficacy and fewer side effects when compared to the older benzodiazepines, for example Pfizer's Xanax, the company wrote.

However, the failure of these drugs so far to establish any real concrete proof of efficacy means this hypothesis looks unlikely to be proven.

According to pipeline data from *EvaluatePharma*, just four CRF1 antagonists are in clinical development whereas 18 pre-clinical or clinical candidates have been abandoned and none have successfully completed phase II trials.

Glaxo's waning enthusiasm

The latest set back means Glaxo is likely to be seriously considering its commitment to this space, particularly given its decision earlier this year to exit neuroscience research (*Glaxo announces cull that could get partners squirming, February 4, 2010*).

Just as well for Neurocrine and its investors then that the company has been on a good run recently, striking a few important deals including Abbott Laboratories' licensing of endometriosis agent, elagolix (*Neurocrine wastes no time delivering deal but hurdles remain, June 16, 2010*). Trading at $5.93 today, the stock is close to a three-year high having doubled in value this year. Despite the threat that three important clinical stage assets could be heading for the R&D dustbin, Neurocrine's shares have only slipped 5% since the setback with GSK561679 was announced.

Neurocrine and Glaxo first signed a deal on the CRF programme back in 2001, agreeing to research the area for up to five years, to identify and develop CRF-R1 and CRF-R2 antagonists. One was already in phase I, NBI-34041, although this was abandoned in 2002 in favour of more promising looking follow-on candidates.

The first tranche of the deal cost Glaxo $25.5m in upfront and early milestones, and the sponsored research portion of this collaboration was completed in 2005.

Neurocrine was working on the area long before the Glaxo deal was signed, first establishing proof of concept back in 1999 with a compound partnered with Janssen. This was ultimately terminated due to safety reasons, and Janssen terminated the collaboration in 2002.

Other riders falling back

For GSK561679, the next major results are not expected till December 2013, from a placebo-controlled, phase II post-traumatic stress disorder study in women, being conducted by Emory University and Mount Sinai School of Medicine.

A phase II comparative pharmacodynamics trial of GSK561679 and GW876008, another GSK/Neurocrine CRF1 antagonist, in IBD patients was terminated in January 2008, the reasons for which are unclear.

Incidentally, GW876008 itself was subject to an investigation by University College London Hospital (UCLH), completed last year, where it was shown to alleviate stress-induced rectal hypersensitivity in a particular sub-set of IBD patients – those where external stress stimuli cause a persistent disinhibition of sympathetic nervous outflow. This is not, however, a characteristic common to all IBD sufferers.

A former leader in the game, Bristol-Myers Squibb via its 2001 acquisition of DuPont Pharmaceuticals, experienced a number of setbacks with its CRF1 antagonists, particularly pexacerfont. The drug reached a phase II/III trial for generalised anxiety disorder, the phase II part completed in March 2008 but failed to achieve the desired efficacy outcomes. Pexacerfont was subsequently abandoned.

Last roll of the CRF dice?

Further interest in the CRF field now turns to data from Sanofi's SSR 125543 programme, which could yet pull this class back into the depression arena. Cowen is the only analyst providing a forecast on the product, predicting a launch in 2013 and sales of $125m by 2015. Looking at the available data though, this looks on the high side of optimistic, and any failure here could signal the end of CRF1 antagonist development for depression.

All in all, the future does not look bright for this target or class of compounds. While Neurocrine may want to champion the mechanism of action, historical and current data do not reflect this enthusiasm. The setback this week only looks like hastening the departure of yet another big pharma company from the field.

CRF-1 receptor antagonists						
Status		**Product**	**Generic Name**	**Company**	**Originator**	**Indication Summary**
Phase II		SSR 125543	-	Sanofi-Aventis	Sanofi-Synthélabo	Depression [Phase II]; Post-traumatic stress disorder [Phase II]; Generalised anxiety [Phase I]
		GW876008	emicerfont	GlaxoSmithKline + Neurocrine Biosciences	Neurocrine Biosciences	Social anxiety disorder [Phase II]; Irritable bowel syndrome (IBS) [Phase II]; Depression [Abandoned - Phase II]
		GSK561679	verucerfont	GlaxoSmithKline + Neurocrine Biosciences	Neurocrine Biosciences	Depression [Phase II]; Generalised anxiety [Phase II]; Irritable bowel syndrome (IBS)

						[Abandoned - Phase I]
Phase I		GSK586529	-	GlaxoSmithKline + Neurocrine Biosciences	Neurocrine Biosciences	Depression [Phase I]; Generalised anxiety [Phase I]; Irritable bowel syndrome (IBS) [Phase I]
Abandoned - Phase II	*Abandon date*					
	2008	Pexacerfont	pexacerfont	Bristol-Myers Squibb	Bristol-Myers Squibb	Generalised anxiety [Abandoned - Phase II]; Depression [Abandoned - Phase II]; Irritable bowel syndrome (IBS) [Abandoned - Phase II]
	2008	ONO-2333Ms	-	Ono Pharmaceutical	Ono Pharmaceutical	Depression [Abandoned - Phase II]; Generalised anxiety [Abandoned - Unclassified]
	-	DPC-368	-	Bristol-Myers Squibb	DuPont Pharmaceuticals	Depression [Abandoned - Phase II]; Generalised anxiety [Abandoned - Unclassified]
	2000	NBI-30775	-	Johnson & Johnson + Neurocrine Biosciences	Neurocrine Biosciences	Depression [Abandoned - Phase II]; Generalised anxiety [Abandoned - Unclassified]