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Therapy focus – Another bet on the small-molecule approach to migraine

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Until recently attempting to treat migraine through the inhibition of pathways involving CGRP was thought to have to involve monoclonal antibodies, and oral therapeutics were thought to be dead in the water owing to a link with serious liver toxicity. Not any more.

A case in point is yesterday's tie-up between Teva and the Sosei unit Heptares that focuses specifically on small molecules. It is likely that Teva – facing the daunting task of restocking its R&D pipeline – was guided by Allergan's $250m endorsement of this approach four months ago (see table below).

That earlier tie-up saw Merck & Co bow out of the small-molecule CGRP inhibition space, selling its two clinical assets, ubrogepant and MK-1602, for $250m up front to the group that will shortly be part of Pfizer. Merck had earlier ditched two clinical-stage oral CGRP inhibitors, telcagepant and MK-3207, over liver toxicity concerns.

Umer Raffat, an analyst with Evercore ISI, points out the curious fact that Allergan did the deal even though there are structural similarities between the current projects and the two that had been scrapped.

Still, Allergan will surely have scrutinised them under its due diligence and satisfied itself of a way forward before handing over $250m. Interestingly, no clinical data have been revealed about ubrogepant or MK-1602, though Merck must have had these in house.

As such the message from Allergan is that this approach might have legs after all. And Teva must have taken this view before striking its deal with Heptares yesterday, notwithstanding the fact that this early-stage alliance is only worth an initial $10m.

Long history

Of course, Teva already has an in-house anti-CGRP agent – TEV-48125 – though this is a MAb, so the group clearly wants two shots on goal.

TEV-48125 has had a long and chequered past, having initially been in development by Rinat Neuroscience as RN-307. When Rinat was bought by Pfizer the MAb was renamed PF-04427429, before being spun out as LBR-101 into Labrys, a new biotech that ended up being bought by Teva for $200m last year.

CGRP (calcitonin gene-related peptide) is a vasodilator produced in peripheral and central neurons, thought to play a central role in in pain transmission and migraine. Teva was encouraged by this approach after TEV-48125 hit primary and secondary phase II endpoints this year, meaning that it had chalked up successes in chronic and episodic migraine alike.

Selected CGRP-targeting migraine projects		
Project	**Company**	**Status**
Anti-CGRP MAbs		
ALD403	Alder Biopharmaceuticals	Phase III
LY2951742	Lilly	Phase III
AMG 334	Amgen/Novartis	Phase III
TEV-48125	Teva Pharmaceutical	Phase II
Small molecules		
Ubrogepant (MK-1602)	Merck & Co/Allergan	Phase II
MK-8031	Merck & Co/Allergan	Phase I
CGRP project	Heptares (Sosei)	Preclinical
Telcagepant (MK-0974)	Merck & Co	Abandoned - Phase III
MK-3207	Merck & Co	Abandoned - Phase II
Olcegepant (BIBN 4096)	Boehringer Ingelheim	Abandoned - Phase II
BI 44370	Boehringer Ingelheim	Abandoned - Phase II
BMS-694153	Bristol-Myers Squibb	Abandoned - Preclinical
Spiegelmer		
NOX-L41	Noxxon Pharma	Preclinical
Unspecified		
Migraine research project	Pharmnovo	Preclinical
Source: EvaluatePharma.		

Nevertheless, the jury is still out over small molecules, and two of these projects were also scrapped by Boehringer Ingelheim. Since MAbs are too big to cross the blood/brain barrier targeting CGRP necessarily takes place outside the brain – theoretically also avoiding CNS-related side effects.

And though Teva is clearly bulking up in this area it is by no means the leader. That honour is shared by Alder, Lilly and Amgen/Novartis, which all have phase III projects (*IHS – Migraine rides to Alder's rescue, May 18, 2015*).

There are further subtleties, such as that of the MAbs only AMG 334 hits the CGRP receptor, while ALD403, LY2951742 and TEV-48125 target the CGRP ligand; all the small molecules appear to target the receptor. Heptares's focus is on G-protein coupled receptor chemistry, incorporating point mutations to aid stability.

If it is undeniable that big companies are betting on CGRP inhibition again there still remains one curious anomaly: why should groups like Merck and Pfizer so willingly ditch projects that, according to Teva anyway, could have peak sales potential of $2-3bn?

And there is an ironic twist, too: when Pfizer completes its $160bn takeover of Allergan it will again be in the possession of anti-migraine assets targeting CGRP.

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