BIOBUSINESS BRIEFS

TRIAL WATCH

Opioid receptor blocker shows promise in Phase II depression trial

Preliminary results from a Phase II trial of Alkermes's ALKS 5461, a therapeutic that acts as a κ-opioid receptor antagonist, indicate that it improves symptoms in patients with major depressive disorder who do not respond to current therapies.

Current antidepressants — selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors and tricyclic antidepressants — all modulate monoamine levels and have limitations that include a lack of effectiveness in a substantial proportion of patients. "About 25–50% of patients have depression that is difficult to treat and probably need drugs or devices that have a new mechanism of action," says Madhukar Trivedi, Professor of Psychiatry and Director of the Comprehensive Center for Depression, University of Texas Southwestern Medical Centre, USA (who has consulted for Alkermes).

According to Charles Chavkin, Professor in the Department of Pharmacology at the University of Washington, Seattle, USA, new antidepressants that target the κ-opioid receptor (like ALKS 5461) could be of particular value for patients who have a stress-induced component in their illness. "Individuals with depression and anxiety have heightened sensitivities to stress exposure, and the endogenous dynorphin opioid peptides that are released following exposure to stress act at κ-opioid receptors," he explains. "In preclinical models, κ-opioid receptor antagonists effectively reduce the anxiety-like and depression-like behaviours caused by stress exposure."

ALKS 5461 is a combination therapy composed of buprenorphine (a κ-opioid receptor antagonist and a μ-opioid receptor agonist that is already approved to treat pain and opioid addiction) and samidorphan, (an investigational μ-opioid receptor antagonist).

"There is a good history of patient exposure to buprenorphine, but because it has weak agonist activity at the μ-opioid receptors (where morphine and oxycodone act), there are risks of sedation and addiction. So combining buprenorphine with a μ-opioid receptor antagonist gives the formulation greater functional selectivity and makes pharmacological sense," says Chavkin.

The Phase II trial assessed the efficacy and safety of ALKS 5461 administered once daily for 4 weeks as an adjunctive treatment in 142 patients. The study met its primary end point of a significant improvement ($p = 0.026$) in depressive symptoms, as measured by the Hamilton Depression Rating Scale (HAM-D17). Detailed data were due to be presented at the Annual New Clinical Drug Evaluation Unit Meeting in Hollywood, Florida, USA, at the end of May.

Based on these data and earlier positive Phase I/II trial results, Alkermes plans to advance ALKS 5461 into Phase III trials, a stage at which there have been several costly failures for novel antidepressants. For example, all trials in the recent Phase III programme for TC-5214, a nicotinic acetylcholine receptor α4β2 subtype modulator developed by Targacept and AstraZeneca, failed despite showing promising results in Phase II trials.

Such failures highlight the challenges in designing and implementing Phase III trials for depression. "These include the need to identify and recruit the most appropriate patient population, using the right assessment tools, and conducting high-quality objective assessments of the patients," says Trivedi.

Non-monoaminergic antidepressants may also offer a more rapid onset of action than current drugs. Trivedi notes that although it is of high interest to see whether patients who do respond to current treatments could benefit from faster-acting antidepressants, determining this would require a very specific study design. "I am not aware of studies that have successfully randomized treatment responders to rapidly acting antidepressants to answer this important question," he says.

Indeed, several drugs that have non-monoamine-based targets are progressing in the clinic (TABLE 1). "The availability of new antidepressants that do not target the monoaminergic system would be very exciting," enthuses Trivedi. "They would aid translational research by allowing us to assess the influence of novel molecular targets on neural circuitry, and would enable us to determine how best to match patients with the most appropriate treatment," he concludes.

Charlotte Harrison

Table 1 | **Non-monoaminergic agents in clinical trials for depression**

Compound	Company	Targets	Phase
Mifepristone	Corcept Therapeutics	Androgen receptors, glucocorticoid receptors, progesterone receptors	III
AZD6765	AstraZeneca	NMDA receptors	IIb
ABT-436	AbbVie	Vasopressin receptors	II
ALKS 5461	Alkermes	Opioid receptors	II
Esketamine	Janssen	NMDA receptors	II
GLYX-13	Naurex	NMDA receptors (glycine site)	II
ADX-71149	Janssen	mGluR2	II
LY2940094	Eli Lilly	Nociceptin (also known as orphanin FQ) receptor	II
MK-6096	Merck & Co.	Hypocretin (also known as orexin) receptor	II
RG1578	Roche	mGluR2	II
RG7090	Roche	mGluR5	II

mGluR; metabotropic glutamate receptor; NMDA, *N*-methyl-D-aspartate. Data were taken from the BioMedTracker database from Sagient Research and the Cortellis database from Thomson Reuters.