

Strategy

The difference between 4 and 5

By **Stephen Hansen**
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In the space of a month, **Addex Pharmaceuticals S.A.** and **Merck & Co. Inc.** have done two deals that help benchmark the value of research-stage and preclinical assets. The valuations of the two deals were determined by market size and the compounds' potential in other indications, in addition to other factors such as medical need and innovation.

Last month, Merck in-licensed Addex's preclinical positive allosteric modulators of metabotropic glutamate receptor subtype 4 (mGluR4) to treat Parkinson's disease (PD) and other undisclosed indications. The deal provided Addex \$3 million up front and up to \$167.5 million in milestones, plus royalties.

Last week, the companies partnered to develop and market ADX63365 and other positive allosteric modulators of mGluR5 to treat schizophrenia and other undisclosed indications. ADX63365 is in pre-clinical development. Addex will receive \$22 million up front and up to \$455 million, plus royalties, for the first compound developed in two indications. For a second compound in two indications, Addex will be eligible for \$225 million in additional milestones, plus royalties.

In both deals, the companies will collaborate on preclinical development, while Merck will be responsible for clinical development. Addex has an option in each case to co-promote resulting compounds in undisclosed EU countries, giving the company an opportunity to establish a sales force.

Merck did not disclose a timeline for when ADX63365 would enter the clinic.

Addex CEO Vincent Mutel said that in both deals, the main drivers for valuing the assets were the same: market size of all potential indications for the compounds and the medical need and/or need for innovation in those indications. Other factors such as competition and the existence of backup compounds played a role as well.

Mutel said the company valued the PD market at around \$1.5-\$2 billion, while the schizophrenia market was significantly larger at \$10-\$15 billion. Of similar importance in valuing these compounds was the market potential of indications outside of PD and schizophrenia.

Although Addex did not disclose other indications, Mutel did say mGluR5 modulators are believed to have potential utility in a broader range of large indications, whereas the mGluR4s may be more restricted in terms of the diseases where they may be of therapeutic use.

Mutel noted both PD and schizophrenia have limited treatment options, so the potential for an innovative approach to both diseases positively influenced the valuations of the deals.

The lack of novel approaches in both disease areas also increased the competition among bidders for Addex's programs.

Merck's SVP of worldwide licensing and external research, Mervyn Turner, agreed with Mutel that the novel mechanisms of the mGluRs were a main driver in the valuation process. He added that the more advanced stage of the mGluR5 program contributed to its higher valuation.

"The marketplace itself of course has a value," he said. "As

you'd do if you were looking to buy a piece of real estate, you'd look to see what a comparable piece of real estate is costing in your location."

Turner also said that Merck considered the strength of the IP, as well as the synergy the mGluR programs would have with Merck's other compounds, although he would not disclose whether the pharma has any compounds in development for schizophrenia.

Although the companies declined to discuss the mechanism of mGluR5 in schizophrenia, two recent papers point to the potential to replace existing drugs.

The pathophysiology of the disease is believed to involve excessive dopamine transmission, especially at dopamine D2 receptors, and glutamate NMDA receptor hypofunction. All marketed antipsychotics block dopamine receptors, and their antipsychotic effects are strongly associated with their antagonism of dopamine D2 receptors.

However, these treatments do not affect the cognitive deficits associated with schizophrenia and are generally associated with side effects including sedation, motor impairment, hormonal side effects such as hyperprolactinemia, and weight gain.

Researchers led by Lucas Lecourtier at the **University of Pittsburgh** showed in a 2007 paper in *Biology Psychiatry* that when rats were given an NMDA receptor antagonist, it impaired brain activity associated with cognitive functions including learning, attention and memory, and the models exhibited similar symptoms to those seen in schizophrenia. However, when the rats were treated with a positive allosteric modulator of mGluR5, the NMDA receptor activity was enhanced, reversing the alterations in brain activity induced by the NMDA receptor antagonists.

Additionally, as reported in a 2005 paper by Gene Kinney and colleagues at **Merck Research Laboratories** in *The Journal of Pharmacology and Experimental Therapeutics*, rats were given amphetamine to induce excessive dopamine release, which is associated with the symptoms of psychosis and cognitive dysfunction in schizophrenia. Subsequent treatment with CDPPB, a positive allosteric modulator of mGluR5, reversed the hyperlocomotion induced by amphetamine, and reversed impairment of prepulse inhibition, which is associated with information processing and cognitive function.

In both papers, the effects of the positive allosteric modulators of mGluR5 were independent of dopamine, indicating the potential for mGluR5 treatments to avoid the side effects associated with dopaminergic therapeutics.

In schizophrenia, it is therefore possible that a positive modulator of mGluR5 could reverse both the effects of excess dopamine and NMDA receptor hypofunction. This would mean that targeting mGluR5 might address both the psychosis and cognitive deficits of the disease.



COMPANIES AND INSTITUTIONS MENTIONED

Addex Pharmaceuticals S.A. (SWX:ADXN), Geneva, Switzerland

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.

Merck Research Laboratories, West Point, Penn.

University of Pittsburgh, Pittsburgh, Penn.