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Neurocrine picks Takeda’s brain

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Neurocrine Biosciences' latest collaboration, with Takeda, gives it three more high-risk bets in neuroscience.

Despite striking a trio of deals last year, Neurocrine still has a thirst for early-stage assets. Yesterday’s deal with Takeda has brought in three clinical – and four preclinical – neuroscience projects, bolstering a pipeline already heavily reliant on external innovation.

The collaboration is a bold move by Neurocrine: all three of the named projects have novel mechanisms and are in tricky indications such as schizophrenia and depression. Still, with its marketed drug Ingrezza still going strong the company has cash to spend, and the agreement has only cost it $120m up front.

Investors seemed to like the deal: Neurocrine’s stock closed up 3% yesterday. The company should be applauded for reinvesting in innovation – the Takeda tie-up is just the latest move in an overhaul that began after Ingrezza failed in Tourette’s in late 2018. In the wake of the flop the group signed a partnership with Voyager Therapeutics to develop CNS gene therapies; this was followed by two deals with Xenon and Idorsia, both covering rare epilepsy projects.

In with the new: Neurocrine's clinical pipeline		
Project	**Indication**	**Description**
Phase II		
NBIb-1817 (VY-AADC)*	Parkinson's disease	AAV gene therapy
Crinecerfont (NBI-74788)	Congenital adrenal hyperplasia	CRF1 antagonist
TAK-831**	Negative symptoms of schizophrenia	D-amino acid oxidase inhibitor
Phase I		
TAK-653**	Treatment-resistant depression	Ampa potentiator
TAK-041**	Anhedonia in depression	GPR139 agonist
NBI-827104 (ACT-709478)^	Epilepsy	T-type calcium channel blocker
NBI-921352 (XEN901)^^	Epilepsy	NaV 1.6 sodium channel blocker
**Under Voyager collaboration; **Under Takeda collaboration; ^Licensed from Idorsia; ^^Under Xenon collaboration. Source: EvaluatePharma, company website.*		

Takeda's motivation is less clear, particularly as the company emphasised neuroscience as one of its core therapy areas during its takeover of Shire. But during yesterday's call Neurocrine's chief executive, Kevin Gorman, stressed that Takeda had not out-licensed the projects and "still wants to be involved" with them; he added that the Japanese company was "definitely not getting out of CNS".

Under the terms of the deal the Japanese company can opt in or out of a 50:50 profit share on an asset-by-asset basis. If Takeda chooses not to opt in, it could earn up to $495m in clinical and $1.4bn in commercial milestones.

Tak it away

For now, Neurocrine is responsible for the development of the projects. TAK-831 is the most advanced, with the phase II Interact study currently recruiting and top-line data expected next year.

The selective D-amino acid oxidase inhibitor is being tested as an adjunctive therapy for the negative symptoms of schizophrenia, such as apathy and blunted emotional responses. The theory behind this approach is that by increasing NMDA activity, DAAO inhibitors could address the NMDA receptor hypofunction that has been linked with schizophrenia.

No drugs are approved specifically for negative schizophrenia symptoms. The only other DAAO inhibitor in clinical trials, according to *EvaluatePharma*, is the Taiwanese company Syneurx's NaBen (sodium benzoate), which is in phase II/III development.

During a conference call yesterday, Neurocrine execs described sodium benzoate as a "much less potent" inhibitor of DAAO than TAK-831.

Still, there are other projects in the schizophrenia pipeline shooting at the same goal, Leerink analysts noted.

Selected pipeline projects for schizophrenia negative symptoms				
Project	**Company**	**Mechanism**	**2026e schizophrenia sales ($m)**	**Note**
MIN-101	Minerva	5HT-2A & sigma-2 antagonist	825	Phase III trial ongoing (NCT03397134)
Nuplazid	Acadia	5HT2A inverse agonist	345	Phase II Advance study completed (NCT02970305)
AVP-786	Avanir	NMDA antagonist, sigma-1 agonist & CYP2D6 enzyme inhibitor	-	Phase II/III ongoing (NCT03896945)
BIIB-104	Biogen	Ampa agonist	10	Phase II ongoing (NCT03745820)
KarXT	Karuna	Muscarinic acetylcholine modulator	657	Phase Ib trial to start 2020
Source: EvaluatePharma, Leerink note June 16, 2020.				

TAK-653 and TAK-041, meanwhile, are both described as phase II ready.

The former is an Ampa potentiator in development for treatment-resistant depression. Ampa has long been linked to depression and other CNS disorders; however, several projects targeting the Ampa receptor have been discontinued due to side effects. Neurocrine plans to use PET ligands to find a therapeutic window for TAK-653, but this looks like a particularly risky bet.

Finally, TAK-041 targets the G-protein coupled receptor 139, which is found in the habenula, an area of the brain involved in the reward system. Neurocrine is planning to evaluate the project in depressed patients with anhedonia, the inability to experience pleasure. The asset was previously in a phase II trial in anhedonia in schizophrenia.

Neurocrine has the lofty goal of being the world's leading neuroscience company and Mr Gorman said during yesterday's call that the group would continue to invest in this area. More deals might be on the cards.