Evaluate Vantage

November 23, 2021

Neurocrine gets selective in schizophrenia

Madeleine Armstrong

The group’s deal with Sosei will see it compete with Karuna and Cerevel.

Sosei’s selective muscarinic agonists, dumped by Abbvie earlier this year, have found a new partner in the shape of Neurocrine Biosciences. Neurocrine hopes that a more selective approach could provide antipsychotic benefits while avoiding the systemic side effects that have limited the potential of more broadly acting muscarinic agents.

The group is not the only one with this idea: notably, Karuna and Cerevel have already reported promising data with their selective agents in schizophrenia. Neurocrine’s move into this space therefore looks like a safer bet than some of its other recent forays, but competition could end up being fierce.

Still, one question is why, if these assets are so promising, Abbvie returned the rights. True, the deal was penned by Allergan in 2016, before Abbvie acquired that group, so the programmes might no longer be a priority.

But Stifel noted “potentially excellent synergies” with Abbvie’s Vraylar franchise. The press release announcing the end of the Abbvie-Sosei deal said the decision was not related to efficacy, safety or other data, perhaps reassuring Neurocrine investors.

$100m up front

In any case, Neurocrine is hardly breaking the bank for its latest deal, at least not initially. It is paying $100m up front, but could also end up shelling out $1.5bn in regulatory milestones.

Approval is some way away: the most advanced asset, HTL-0016878, is set to go into phase 2 in schizophrenia next year. Neurocrine has also gained rights to preclinical M4, M1 and M1/M4 agonists in development for various CNS disorders. Sosei will retain rights to M1 agonists in Japan.

The rationale behind this approach is clear: current antipsychotics primarily target dopamine, but are linked with side effects such as weight gain and do not work in all patients, so there is a need for new agents.

Targeting the muscarinic cholinergic system, for example with the M1 and M4 agonist xanomeline, has previously shown promise. However, this came at the price of adverse events including nausea, vomiting, diarrhoea and sweating, thought to be linked with stimulation of peripheral muscarinic receptors.

PANSS people

The lead proponent of the selective muscarinic approach, Karuna, is trying to solve this problem by combining xanomeline – which it licensed from Lilly – with trospium chloride, a muscarinic antagonist that does not cross the blood-brain barrier. The idea is that the latter cancels out xanomeline's peripheral adverse events but does not hamper its effects in the brain.

A phase 2 trial of the group's contender KarXT met its primary endpoint, with KarXT decreasing positive and negative syndrome scale (PANSS) scores by 11.6 points on a placebo-adjusted basis. Cholinergic and anticholinergic side effects were still seen with KarXT, but discontinuation rates were similar across the treatment and placebo groups, the authors noted.

Karuna is due to report pivotal data on KarXT next year. The group is also planning pivotal trials in schizophrenia patients with an inadequate response to current therapy, and Alzheimer's disease psychosis.

Meanwhile, Cerevel, like Neurocrine, hopes that being more selective could minimise side effects without the need for combination therapy. Cerevel recently reported similarly promising PANSS data from a phase 1 data with its contender, the M4 positive allosteric modulator CVL-231 (*Cerevel finds trial success as easy as '231, June 29, 2021*).

Encouragingly, rates of nausea and other gastrointestinal adverse events were similar with the asset and placebo. More details on Cerevel's phase 2 plans are expected next quarter.

Other groups in this space include Acadia and Takeda, which both have M1 positive allosteric modulators in development, although the latter's TAK-071 is being evaluated in Parkinson's rather than schizophrenia.

Neurocrine and Takeda are already partners, but that deal has not gone smoothly so far, with one of the assets involved, luvadaxistat, failing a phase 2 study in schizophrenia negative symptoms earlier this year. Neurocrine will have to hope that it has picked a more promising avenue with its latest deal.

Selected selective muscarinic receptor agonists in development for CNS disorders

Project	Company	Description	Trial info
Phase 3			
KarXT (xanomeline + trospium)	Karuna Therapeutics	M1/M4 agonist + muscarinic receptor antagonist	Emergent-2 & Emergent-3 in schizophrenia; data due mid-2022 and H2 2022 respectively
Phase 2			
TAK-071	Takeda	M1 positive allosteric modulator	NCT04334317 in Parkinson's, ends Nov 2022
Phase I			
CVL-231	Cerevel Therapeutics	M4 positive allosteric modulator	Positive ph1 data in schizophrenia reported Jun 2021
HTL-0016878	Neurocrine/Sosei Heptares	M4 agonist	Ph2 in schizophrenia to start 2022
ACP-319	Acadia Pharmaceuticals	M1 positive allosteric modulator	For schizophrenia & cognitive impairment in Alzheimer's; ph1 multiple ascending dose study initiated
Source: Evaluate Pharma & clinicaltrials.gov.			