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Sosei, Neurocrine ink $2.6B neuropsychiatric collaboration

By Nuala Moran, Staff Writer

LONDON – Sosei Heptares is to get $100 million up front in a potential $2.6 billion deal with Neurocrine Biosciences Inc., in which the pair will develop muscarinic receptor agonists in the treatment of schizophrenia, dementia and other neuropsychiatric disorders.

San Diego-based Neurocrine is taking rights to a portfolio of small molecules against specific subtypes of the muscarinic receptor family, targeting M1 and M4 alone, plus a dual M1/M4 agonist.

This is the second time Sosei Heptares has out-licensed these assets. The first taker in April 2016, was Allergan plc, which paid $125 million up front, in an agreement with a headline value of $3.3 billion. The rights were returned to the Cambridge, U.K.-based company in January this year, following completion in May 2020 of Abbvie Inc.'s acquisition of Allergan and a subsequent pipeline reorganization.

Allergan invested more than $55 million during the four or so years it was in charge of the portfolio. Sosei Heptares got back eight programs, together with associated intellectual property and clinical data generated in that time. That includes three programs with phase I data.

The most advanced of those programs, HTL-0016878, an M4 agonist, was safe and well-tolerated in a phase I trial in 120 healthy volunteers. It will now be lined up for a phase II placebo-controlled study in schizophrenia sponsored by Neurocrine that will start in 2022.

Muscarinic receptors are G protein-coupled receptors (GPCRs) that are validated as targets in psychosis and cognitive disorders. In particular, Sosei Heptares points to Karuna Therapeutics Inc.'s Karxt, an M1/M4 agonist that has turned in proof of concept in a double-blind, placebo-controlled trial in schizophrenia, and to Cerevel Therapeutics Inc.'s CVL-231, for which positive top-line results from a phase Ib study in schizophrenia were published in June 2021.

Those have reawakened investors and the pharma industry's awareness to the potential of drugs targeted at muscarinic receptors in the treatment of psychosis and cognition, according to Sosei Heptares. It said the selectivity of its molecules will avoid the harmful gastrointestinal and cardiovascular side effects of non-selective agonists, while having potential for greater therapeutic effect.

The selectivity rests on Sosei Heptares' technology for stabilizing GPCRs, which opens them up for structure-based drug discovery.

Sosei Heptares' parent company, Tokyo-based Sosei Group Corp., retains the rights to develop M1 agonists in Japan, in all indications, with Neurocrine receiving co-development and profit-share options.

Of the $2.6 billion headline value of the deal, $1.1 billion is in development and regulatory milestones up to approval. A further $1.1 billion hangs upon achieving certain global sales milestones. There will then be royalties ranging from high single-digit to midteen percentage on net sales.

In addition, Neurocrine is to fund R&D carried out by Sosei Heptares through phase I studies.

Familiar territory

Malcolm Weir, chief R&D officer, Sosei Heptares

Neurocrine will be a good new home for the portfolio, said Malcolm Weir, chief R&D officer of Sosei Heptares. "They're a terrific partner. First of all, they're very science driven. They have a heritage in GPCRs, they're focusing on neuroscience, they've got a great track record in developing molecules, alone, and in partnership," he said.

In addition, Neurocrine has a marketed product, Ingrezza (valbenazine), for treating tardive dyskinesia, the movement disorder which affects a high percentage of those schizophrenia patients who take dopamine antagonists long term to prevent psychosis.

Neurocrine also is developing d-amino acid oxidase inhibitor luvadaxistat, (also labelled NBI-1065844 and TAK-831) in schizophrenia, with partner Takeda Pharmaceutical Co. Ltd., of Tokyo. In data published in March this year, luvadaxistat missed the primary endpoint of change from baseline in symptoms score at day 84, but hit secondary endpoints in the phase II study relating to cognitive assessment.

The "totality of the top-line data" support further clinical evaluation of luvadaxistat, Neurocrine said, when the results were announced.

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Luvadaxistat was one of seven programs, including three clinical-stage assets for schizophrenia, treatment-resistant depression and anhedonia, to which Takeda gave Neurocrine an exclusive license in June 2020.

"This is very familiar territory to them," Weir told *BioWorld*.

A "reasonably conservative estimate" is that the M1 and M1/M4 programs will follow HTL-0016878 into further clinical development in 2023. As yet, the indications are not decided, but Weir said Alzheimer's disease, dementia with Lewy Bodies, bipolar disorder and schizophrenia are all in the cards.

A joint steering committee will make those decisions. "We'll share our thoughts and information; it's in everybody's interest to go for the best indication, what's most likely to work, and where the market is most clearly defined. The ones I mentioned are in pretty dire need of new entrants," said Weir.

Assuming the transaction closes as expected before the end of the year, Sosei Heptares will recognize the $100 million up-front payment this financial year. There will be several "material milestones" over the next 24 to 36 months assuming INDs on the programs are filed and things move forward, said Chris Cargill, chief financial officer.

"[This] will certainly enable us to invest more in bringing forward a number of prioritized in-house programs that we have across our core therapeutic areas, which are neurology, immunology and gastrointestinal [diseases]," Cargill said. "We've already identified those programs and, of course, the up-front that we will receive from this transaction today will just simply enable us to move those forward faster," he told *BioWorld*.

Chris Cargill, chief financial officer, Sosei Heptares

Both Weir and Cargill stressed the importance for Tokyo-listed Sosei Corp. of retaining rights to develop M1 agonists in its domestic market of Japan. Neurocrine will have two opportunities to opt-in and co-develop those programs: at the point when a phase II trial is approved, or when the data from the trial readout.

Sosei was previously poised to start a phase II trial of an M1 agonist, HTL-0018318, in Lewy body dementia in Japan, but that was pulled in September 2018 after cynomolgus monkeys in a toxicology study run by Allergan developed neoplastic tumors.

The tumors occurred at doses and durations exceeding those used in the approximately 310 healthy volunteers, and in patients with mild to moderate Alzheimer's, who had received the drug. In follow-up, there have been no clinical findings of concern, but the trial remains on hold. Sosei Heptares is now advancing other M1 agonists with new chemistry.

"We got so close and then had a setback," Weir said. "These things happen in drug development. But what we did do in the phase I and phase Ib studies that we conducted [was to] really build a deeper knowledge of the potential for the general mechanism."