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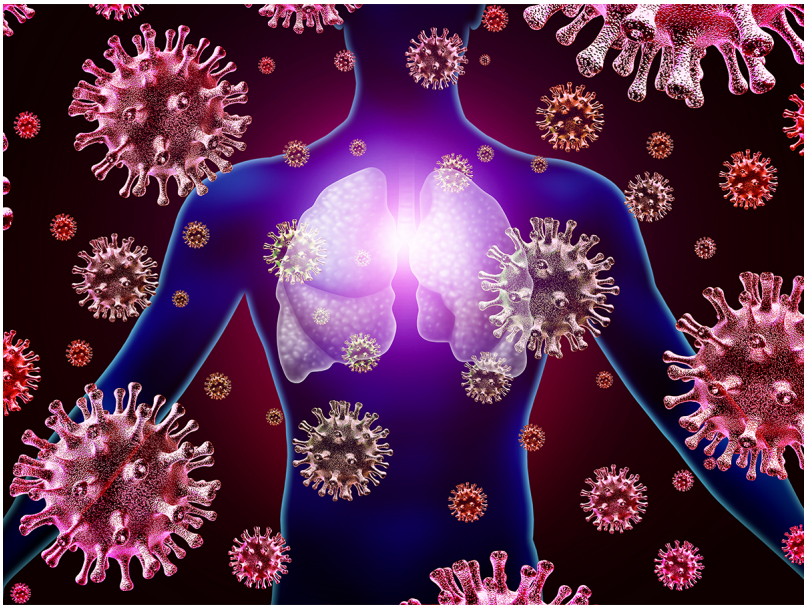

Taiwan's Syneurx gears up for phase III test of COVID-19 oral antiviral

By Tamra Sami (/authors/49-tamra-sami)
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Following the readout of a phase II trial evaluating its COVID-19 oral antiviral Pentarlandir (https://www.cortellis.com/intelligence/report/ci/nextgendrugall/131108) (SNB-01), Taiwan's Syneurx International Corp. (https://www.cortellis.com/intelligence/report/ci/company/1086582) said it expects to launch a phase III test of the candidate in the next few months.

In the phase II trial (https://clinicaltrials.gov/ct2/show/NCT04911777), 89 participants with breakthrough or unvaccinated cases of COVID-19 were randomized across high-dose, low-dose and placebo groups. The results showed that Pentarlandir reduced inflammation caused by the SARS-CoV-2 virus and improved overall health.

For the primary endpoint of change in viral load during the 14-day treatment period, there was no significant difference in viral load between the high-dose group (-6.2) and the placebo group (-8.1) on day 14, and the p-value of the difference between the low-dose group and the placebo group was 0.1070.

"Viral count is one outcome, and we also did a few clinical outcomes including inflammatory markers," Syneurx Founder and CEO Emil Tsai told *BioWorld*.

> "We can deal with infection and the immune system, but inflammation is out of check when the body system is trying to meet the challenge of the invasion of the virus," he said, noting that six major inflammatory outcomes were studied, and the majority of

Emil Tsai, founder and CEO, Syneurx

those were positive. "COVID will be around for a while, so it's important that we saw improvement in clinical outcomes and inflammatory outcomes."

Secondary endpoints showed encouraging trends in the treatment group, including greater improvement in overall health status and a reduction in total COVID-19 symptoms compared to the placebo group. On average, Pentarlandir-treated groups were associated with less days of worsening symptoms in half of the 24 COVID symptoms measured.

Pentarlandir was well-tolerated in both high- and low-dose groups with no serious adverse events. There were a limited number of adverse events overall (15%), most of which were mild. Only a few cases (4%) were related to the treatment drug.

Competitive landscape

The compound is designed for the majority of COVID-19 patients who are in general good health with little risk of progressing to severe COVID-19. In contrast, Pfizer Inc (https://www.cortellis.com/intelligence/report/ci/company/18767)'s antiviral Paxlovid (https://www.cortellis.com/intelligence/qsearch/paxlovid) (nirmatrelvir + ritonavir) is designed for those who are at high risk of developing serious COVID-19 complications.

Pentarlandir is a D-amino acid oxidase (DAAO) inhibitor, which modulates N-methyl-D-aspartate (NMDA) receptors and protects neurons in the brain. This means the candidate could potentially improve post-COVID-19 conditions such as depression and cognitive deterioration.

It works against SARS-CoV-2 by inhibiting the main protease of SARS-CoV-2 to suppress virus replication and by inhibiting the transmembrane protease serine 2 (TMPRSS2) of human cells to block virus entry. It also provides an anti-inflammatory effect against the cytokine storm that can lead to more serious illness.

Given the natural origins of Pentarlandir's active chemical component, costs for the drug are expected to be significantly lower than for Paxlovid.

If successful, Syneurx intends to make Pentarlandir available to the world's developing nations as part of the United Nations-backed Medicines Patent Pool.

"Given the worldwide onslaught of the omicron variant of COVID-19 plus its ability to substantially evade current vaccines and its proclivity to manifest as a less-lethal endemic virus than its predecessors, the need for an inexpensive and highly effective oral antiviral has never been greater," Tsai said.

As Pentarlandir is purified from a botanical, the company plans to pursue the Chinese medicine regulatory pathway for Asia. Because it has been documented in the Chinese pharmacopeia for more than 600 years, the product will likely be launched in Asia much sooner than in the U.S. where the company is pursuing a new chemical entity pathway.

Syneurx is seeking partners for its phase III COVID-19 study.

Two platforms

Syneurx's pipeline consists of two platforms – an antiviral platform and its NMDA platform.

While conducting research at Massachusetts General Hospital in 1999, Tsai was the first scientist to report that enhancing the NMDA system could reduce symptoms of neurological disorders. The NMDA receptor regulates cognition, memory, personality, range of emotion, problem solving, personal drive and decision making.

Excessive activation or under-activation of the NMDA receptors contribute to the formation and progression of various CNS disorders including schizophrenia, depression and Alzheimer's disease.

A practicing psychiatrist and neuroscientist, Tsai is especially interested in tackling debilitating conditions like schizophrenia, dementia and depression. Many of these conditions are exacerbated by stress.

"Glutamate is the most abundant neurotransmitter in the brain. Unlike dopamine and serotonin receptors that are restricted to well-defined pathways in limited parts of the brain, glutamate signaling occurs throughout the brain," Tsai said.

"The complex glutamate system is controlled by three types of receptors, with NMDA receptors being the most important, complicated, and delicate ones. Thus, the NMDA system likely functions as the key control knob of the glutamate neurotransmission activities in the brain.

"NMDA is responsible for cognition and learning and memory, and we don't have a drug that helps with that yet, so we are pioneers in this area," Tsai said.

Most of the drugs that treat schizophrenia are dopamine blockers that were developed nearly 60 years ago. They also come with side effects that result in negative symptoms, meaning something is missing, such as emotional flatness, he said.

The company's most advanced pipeline is in schizophrenia. It has three ongoing phase III trials – Naben for adult schizophrenia and adolescent schizophrenia, and Clozaben for refractory schizophrenia.

The NMDA system can be modulated by three mechanisms of action:

D-amino acid oxidase (DAAO) inhibitors maintain or increase the cellular level of D-serine by inhibiting its degradation by DAAO. Naben, Clozaben and Tanquilynne are DAAO inhibitors.
Glycine transporter (GlyT-1) inhibitors block glycine reuptake in order to build up synaptic glycine levels that can enhance the NMDA function. Synapsinae is a GlyT-1 inhibitor; and
NMDA-glycine site modulators like Synxyrin works as a partial antagonist.

Naben is also in a phase II/III trial in early dementia, and Tannquilynne is beginning a phase II trial in dementia with psychosis.

The company has two candidates in depression. Synapsinae is in a phase III trial for depression and suicidality and Synxyrin is in phase II for refractory depression.

Drugs to treat depression often take up to four weeks before an effect is seen, and Tsai said that both drugs to treat depression act in one week and have a more favorable safety profile with less side effects than current drugs on the market.

Founded in 2013, Syneurx listed on the Taipei stock exchange (TPEX:6575) in January 2016. It raised $14.3 million through a public offering in June 2021 to fund development of its schizophrenia trials and COVID-19 trials. The company has about 50 employees, who are mostly engaged in R&D in Taiwan. It also has operations in Torrance, Calif.