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Kynexis: Lowering kynurenic acid levels to improve cognitive function

Dutch biotech's KAT2 inhibitor for cognitive impairment associated with schizophrenia is backed by nine-figure series A

BY LINDSAY MARTIN, BIOPHARMA ANALYST

Dutch biotech Kynexis is testing whether lowering kynurenic acid in the brain can improve cognition in people with schizophrenia, an aspect of the disease largely untouched by dopamine-blocking antipsychotics.

To do so, Kynexis B.V. is pairing an upstream mechanism designed to modulate both glutamatergic and cholinergic signaling with a tightly controlled trial design. Its lead asset, KYN-5356, has completed enrollment in a Phase II study that keeps patients in an inpatient setting and uses blood testing to verify exposure to background antipsychotics, reducing adherence-related variability.

Last week, the company closed a $46 million (€40 million) extension of its series A round, led by Novartis Venture Fund, which brought the financing to $107 million. Existing investors in the Asia-to-West NewCo — Forbion, Ysios Capital, and Sunstone Life Science Ventures — also participated.

Cognitive impairment associated with schizophrenia (CIAS) remains without an approved therapy after a series of failures, including several glutamatergic strategies designed to enhance NMDA receptor function.

Iclepertin, a GlyT1 inhibitor from Boehringer Ingelheim GmbH designed to increase glycine at the NMDA receptor's co-agonist site, missed cognition and functioning endpoints across all three trials of the Phase III CONNEX program. With 1,840 patients, CONNEX was the largest CIAS program conducted to date, and Boehringer discontinued its long-term extension after reporting top-line results in January 2025.

At least three other programs have missed Phase II endpoints in the past two years: luvadaxistat, a DAAO inhibitor that increases NMDA receptor co-agonist D-serine; inidascamine (formerly RL-007), a mixed glutamatergic, cholinergic, and GABA-B modulator from Recognify Life Sciences Inc.; and, most recently, ALTO-101, a transdermally delivered PDE-4 inhibitor from Alto Neuroscience Inc. (NYSE:ANRO).

Kynexis is betting that both the biology and the execution of its program will produce a different outcome. Rather than supplying a single NMDA co-agonist, KYN-5356 works upstream. The molecule inhibits KAT2, an enzyme that produces kynurenic acid (KYNA), a tryptophan metabolite that antagonizes both NMDA and α7 nicotinic acetylcholine receptors (CHRNA7). The goal is to relieve this endogenous inhibition. KAT2 inhibition has also increased extracellular

glutamate in preclinical models, giving the molecule multiple potential routes to strengthen signaling involved in cognition.

"There's a very strong correlation between levels of KYNA and cognitive function," CEO Kees Been told BioCentury. About 80% of people with schizophrenia have a cognitive deficit, and in people with schizophrenia, KYNA levels in cerebrospinal fluid (CSF) are elevated by about 60% on average, he said. Analyses of postmortem brain tissue have also found increased KAT2 expression and higher KYNA levels in people with schizophrenia than in healthy individuals.

"IF YOU WANT TO TRULY SHOW THAT YOUR COMPOUND HAS A PRO-COGNITIVE EFFECT, YOU HAVE TO DOSE IN STABLE PATIENTS."
KEES BEEN, KYNEXIS

Japan's Tanabe Pharma Corp. discovered KYN-5356 but shelved the preclinical asset after exiting psychiatry in 2016. Investor Peter Høngaard Andersen identified the molecule while a venture partner at Ysios Capital. After joining Forbion as an operating partner, he helped the firm in-license the asset and launch Kynexis with Ysios in 2022, becoming the biotech's executive chairman.

"In schizophrenia, you have two reasons for failure: you have a compound failure, because the biology didn't work, or you have what I call trial failure," Been said, attributing the latter to poor patient compliance.

In a first-in-human study in healthy volunteers, seven days of oral KYN-5356 produced dose-dependent reductions in CSF KYNA and increases in quantitative EEG cortical excitability, a pharmacodynamic measure associated with glutamatergic and cholinergic signaling. The compound also increased CSF glutamate. At 800 mg once daily, participants improved 3.2 points more than the placebo group on the tablet-administered Brief Assessment of Cognition, or BAC App, after six days.

Been called the reduction in CSF KYNA the "primary proof that we had target engagement." The tolerability, pharmacodynamic findings, and exploratory cognitive signal supported advancement into Phase II, he said. The BAC App is the current study's primary endpoint, while EEG measures are exploratory. Data are expected by year-end.

The Phase II study does not screen patients for elevated CSF KYNA because Kynexis believes requiring lumbar punctures would impede recruitment and undermine early trust. The cognitive signal in healthy volunteers also suggested that elevated KYNA might not be necessary for a response. The decision facilitates enrollment but forgoes an opportunity to test whether the biomarker could enrich for responsive patients.

Instead, Kynexis is controlling other potential sources of variability. The study enrolls clinically stable patients with stable cognitive deficits and detectable blood levels of their background antipsychotics. Participants remain at inpatient sites throughout the 28-day dosing period, allowing investigators to monitor adherence and separate a direct cognitive effect from improvement resulting from better control of psychosis.

"If you want to truly show that your compound has a pro-cognitive effect, you have to dose in stable patients. You cannot have the risk of a pseudoefficacy signal where, because you get your hallucinations under control, that of course will have some effect on cognition," Been said.

If successful, KYN-5356 could become the first KAT2 inhibitor to reach the market and the first therapy approved specifically for CIAS. According to BioCentury's BCIQ database, no other KAT2 programs are in the clinic.

Kynexis plans to follow the current study with a Phase IIb trial in CIAS. It also plans to test KYN-5356 in healthy older volunteers as an initial step toward Alzheimer's disease, where CSF KYNA levels are also elevated. Been noted there are "correlations established between KYNA levels and tau."

COMPANY PROFILE

Kynexis B.V. (Kynexis Therapeutics Inc.)

Naarden, Netherlands

Technology: Oral small molecule KAT2 inhibitor for cognitive impairment associated with schizophrenia

Origin of technology: In-licensed from Tanabe Pharma Corp.

Disease focus: Neurology

Clinical status: Phase II

Founded: 2022 by Forbion and Ysios Capital

Academic collaborators: None

Corporate partners: None

Number of employees: Not disclosed

Funds raised: $107 million

Investors: Forbion, Ysios Capital, Novartis Venture Fund, Sunstone Life Science Ventures

CEO: Kees Been

Issued Patents: Not disclosed

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