and October 31, 2018 (index date) vs. patients who did not register for dCBTi but initiated a second prescription for an insomnia medication in the same time period (controls). Observation period was 16–24 months. No other inclusion/exclusion criteria were used. Control patients were matched using a nearest neighbor within-caliper matching without replacement approach. Incidence rates for HCRU encounter type were calculated using a negative binomial model for both cohorts. Costs were estimated by multiplying HCRU by published average costs for each medical resource.

Results. Evaluated were 248 cases (median age 56.5 years, 57.3% female, 52.4% treated with sleep-related medications) and 248 matched controls (median age 55.0 years, 56.0% female, 100.0% treated with sleep-related medications). Over the course of 24 months post-initiation, cases had significantly lower incidences of inpatient stays (55% lower, IRR: 0.45; 95% CI: 0.28–0.73; P=0.001), significantly fewer emergency department (ED) visits without inpatient admission (59% lower; IRR: 0.41; 95% CI: 0.27–0.63; P<0.001), and significantly fewer hospital outpatient visits (36% lower; IRR: 0.64; 95% CI: 0.49–0.82; P<0.001). There was also a trend for fewer ambulatory surgical center visits (23% lower; IRR: 0.77; 95% CI: 0.52–1.14; P=0.197) and fewer office visits (7% lower; IRR: 0.93; 95% CI: 0.81–1.07; P=0.302) with the use of SHUTi. Use of sleep medications was more than four times greater in controls vs. cases, with 9.6 (95% CI: 7.88–11.76) and 2.4 (95% CI: 1.91–2.95) prescriptions/patient, respectively (P<0.001). All-cause per-patient HCRU costs were $8,202 lower over 24 months for cases vs. controls, driven primarily by a lower incidence of hospitalizations (-$4,996 per patient) and hospital outpatient visits (-$2,003 per patient).

Conclusions. Patients with chronic insomnia who used a digital CBTi treatment had significant and durable real-world reductions in hospital inpatient stays, ED visits, hospital outpatient visits, and office visits compared to matched controls treated with medications.

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Efficacy and Safety of Iclepertin (BI 425809) in Patients With Schizophrenia: CONNEX, A Phase III Randomized Controlled Trial Program

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Abstract

Introduction. Cognitive impairment is a major determinant of poor functional outcome in schizophrenia and there are currently no available pharmacotherapies. Deficits in glutamatergic signaling play a key role in the neuropathology of cognitive symptoms. Iclepertin (BI 425809), an inhibitor of glycine transporter-1, enhances glutamatergic signaling by increasing synaptic levels of the *N*-methyl-D-aspartate receptor co-agonist, glycine. A 12-week, Phase II trial (NCT02832037) in 509 patients with schizophrenia demonstrated that iclepertin was well tolerated and significantly improved cognition. The Phase III CONNEX program aims to confirm the efficacy, safety, and tolerability of iclepertin in improving cognition and functioning in a larger cohort of patients.

Methods. CONNEX consists of three replicate randomized, double-blind, placebo-controlled parallel-group trials in patients with schizophrenia (NCT04846868, NCT04846881, NCT04860830) currently stable on antipsychotic treatment. Each trial aims to recruit ~586 patients, 18–50 years old, treated with 1–2 antipsychotic medications (≥12 weeks on current drug; ≥35 days on current dose prior to treatment), who have functional impairment in day-to-day activities, and interact ≥1 hour per week with a designated study partner. Patients with cognitive impairment due to developmental, neurological, or other disorders, or receiving cognitive remediation therapy within 12 weeks prior to screening, will be excluded. Patients will be recruited from multiple centers across 32 countries in Asia, North and South America, and Europe, and randomized 1:1 to receive either oral iclepertin 10 mg (n=293), or placebo (n=293) once daily over 26 weeks. The primary efficacy endpoint is change from baseline (CfB) in the MATRICS Consensus Cognitive Battery overall composite T-score. Key secondary efficacy endpoints are CfB in Schizophrenia Cognition Rating Scale total score and CfB in the adjusted total time in the Virtual Reality Functional Capacity Assessment Tool. Long-term safety and tolerability data will be collected in an open-label safety extension study (CONNEX-X).

Results. The studies are currently recruiting (first patients enrolled Aug–Sept 2021), with completion expected in Q2 2024. Here we present an overview of the current study status, including any information relating to screening failures, and the experience of collecting these data as part of a large multi-country, multi-center study.

Conclusion. To date, most large, industry-sponsored studies testing various compounds to address cognitive function have failed to show proof-of-clinical concept. Demonstration of efficacy of iclepertin in improving cognition in this Phase III program would provide important insight into the role of glutamate in cognitive symptoms that may also have relevance for other cognitive disorders. Iclepertin may represent the first efficacious medication for cognitive impairment associated with schizophrenia.

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