Identification of meaningful cognitive endpoints in studies of pharmacological therapies for cognitive impairment in schizophrenia

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The Methodological Question Being Addressed: Can a 'Learn and Confirm' approach be used to identify one or more meaningful cognitive endpoints as a pre-specified primary endpoint in clinical trials?

Introduction (Aims): Specifying the primary endpoint in proof-of-concept trials assessing cognitive impairment associated with schizophrenia (CIAS) presents unique challenges. Endpoints such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) test individual domains (which may come with risk of signal by chance due to testing multiplicity, unless domains are pre-specified), while the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) uses a composite score (with the risk that not all domains are sufficiently improved to show overall significance, or that certain domains will add noise to the data).

This study (NCT02281773) was performed to identify meaningful cognitive endpoints in Stage 1 ('Learn'), allowing pre-specification of the primary endpoint for Stage 2 ('Confirm'), which aimed to show superiority of BI 409306 (a potent, selective phosphodiesterase-9 inhibitor) over placebo.

Methods: This was a multicenter, double-blind study, investigating the efficacy, safety, and tolerability of BI 409306 in patients with schizophrenia. Patients (n=516) were randomized (2:1:1:1:1) to one of five 12-week treatments (once-daily placebo, BI 409306 10−100 mg), with a 4-week follow-up.

Results: The primary efficacy endpoint was defined as change from baseline in cognitive function as indicated by ≥1 CANTAB measurements, or the composite score of MCCB, after 12 weeks of treatment. The key secondary efficacy endpoint was change from baseline in everyday functional capacity, measured by Schizophrenia Cognition Rating Scale (SCoRS) total score, after 12 weeks of treatment. Additional secondary efficacy endpoints included the Patient Global Impressions-Improvement scale score, and change from baseline in MCCB score, Clinical Global Impressions-Severity scale score, and Positive and Negative Syndrome Scale negative symptom factor score, after 12 weeks of treatment. Safety assessments comprised adverse event monitoring, physical examinations, vital signs, cardiac function assessments, and monitoring of clinical laboratory assessments.

In Stage 1, 120 patients (each BI 409306 treatment arm, n=20; placebo, n=40) were randomly selected and their CANTAB data unblinded after 70% of patients completed the treatment period. Change from baseline was investigated by analysis of covariance on seven cognition domains (processing speed, verbal learning, working memory, reasoning and problem solving, attention/vigilance, visual learning, and social cognition), assessed by eight CANTAB measurements. Endpoint(s) differentiating between effects of BI 409306 and placebo would be pre-specified as the endpoint(s) for Stage 2, with analyses based on patients not assessed in Stage 1. If no CANTAB endpoints differentiated between treatment effects, MCCB would be chosen as the primary endpoint. The primary endpoint(s) and an *a priori*

hypothesis testing order were pre-specified before database lock and unblinding. The restricted maximum likelihood based mixed model repeated measurement will be performed on the selected endpoint(s).

Conclusions: This 'Learn and Confirm' approach can be used to identify meaningful cognitive endpoints for use as pre-specified endpoints in investigating potential CIAS treatments.

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