BI 425809 once daily in patients with schizophrenia: Feasibility of novel endpoints to assess motivation

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Is it feasible to use the balloon effort task (BET) and probabilistic reversal learning task (PRLT) to assess the impact of BI 425809 on motivation and flexible learning in patients with cognitive impairment associated with schizophrenia (CIAS) in a large, multicenter, clinical trial?

Introduction Currently, no pharmacotherapy is approved for CIAS. N-methyl-D-aspartate (NMDA) receptor hypofunction is believed to be the underlying pathophysiology leading to CIAS. BI 425809, a glycine transporter-1 inhibitor, in development for treatment of CIAS, elevates the concentration of glycine (NMDA co-activator) in the synaptic cleft, and may improve cognitive deficits. Preclinical and clinical studies suggest that this mechanism of action may also enhance motivational deficits that often accompany CIAS. To evaluate this possibility, the BI 425809 Phase II trial (NCT02832037) assessed two aspects of motivation, effort valuation, and reward learning, using the BET and PRLT, which are rarely used outside of academic research. The aim of the analyses presented here was to explore the feasibility and validity of the BET and PRLT in the context of a large multicenter trial in patients with schizophrenia.

Methods This Phase II, double-blind, parallel-group study randomized patients (1:1:1:1:2) with schizophrenia to oral BI 425809 (2, 5, 10, and 25 mg) or placebo, once daily for 12 weeks. In addition to clinical endpoints of cognition, computerized BET and PRLT were evaluated (US sites only). Academic versions of the BET and PRLT were used, with some adaptation of the BET. Patients completing the BET chose whether to complete an easy or hard task for a low- or high-potential reward, respectively. Patients were shown the potential reward associated with each task at the start of each trial and chose which to complete. Patients completing the PRLT chose between two stimuli (one commonly and one rarely rewarded). Once the patients learned the more frequently rewarded stimulus, the reward contingencies reversed, and patients had to modify their value representations through feedback.

Results Overall, 509 patients were randomized across 11 countries. Among the US population, 194 and 200 patients completed the BET and PRLT, respectively. Baseline scores are shown in Table 1. Both tasks were well tolerated. Mean proportions of difficult choices across the three reward values in the BET were comparable to prior studies. Patients selected difficult choices more frequently for 100% reward probability trials than for 50% reward probability trials. The task did not demonstrate a ceiling effect. There were no significant clinical symptom differences between patients who selected all difficult tasks compared with those who varied their choice (Table 2). Patients who completed 0 initial discriminations (non-learners) in the PRLT demonstrated worse cognition than those who completed ≥1 discriminations (learners). There were no differences in clinical symptom

severity between subgroups (Table 2).
[Table to be inserted by Secretariat]

Conclusion The BET shows promise for clinical trial use though the difficulty level of the PRLT raises some concerns about this measure. Inclusion of these novel measures in the BI 425809 Phase II trial will enable us to further evaluate their reliabilities and sensitivity to treatment.

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Guidelines I have read and understand the Poster Guidelines

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COI
Hake S, Huang S, Zhao Y and Podhorna J are all employees of Boehringer Ingelheim. Horan B, Keefe

R and Atkins A are employees of VeraSci, which provides services for over 100 entities, mostly pharmaceutical companies, including Boehringer Ingelheim. Keefe R is also a consultant for Boehringer Ingelheim.

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Disclosures:

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