Efficacy of BI 425809 in patients with schizophrenia: Phase II trial using a multiple comparison procedure and modeling approach

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Which dose(s) of BI 425809, if any, are more efficacious than placebo for the treatment of cognitive impairment in patients with schizophrenia, as evaluated using a multiple comparison procedure and modeling (MCPMod) approach?

Introduction Cognitive impairments associated with schizophrenia (CIAS) predict poor functional outcomes, but currently no approved treatments are available. This proof-of-clinical-concept (PoCC) and dose-finding (DF) study evaluated treatment of CIAS with the glycine transporter-1 inhibitor BI 425809 using an MCPMod approach with mixed model repeated measures (MMRM) that allows evaluation of PoCC and the assessment of suitable dose(s) in one trial. The statistical analysis compares a wide range of potential dose–response relationships via optimal test contrasts, providing better modeling flexibility for dose estimation, while increasing the probability of success compared with conventional pairwise comparison procedures.

Methods This Phase II, randomized, double-blind, placebo-controlled, parallel-group trial randomized stable outpatients with schizophrenia (aged 18–50 years) to BI 425809 2, 5, 10, or 25 mg or placebo (1:1:1:1:2), added to standard of care. The primary outcome was change from baseline in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) overall composite T-score at Week 12. The MCPMod with MMRM approach was used to evaluate PoCC and to help define suitable dose(s) for further development. Several plausible dose–response models were simultaneously compared to identify the best-fitting model(s), while maintaining full control of the overall family-wise type I error rate (one-sided $\alpha=0.05$) by including data from all treatment groups. PoCC was established if ≥ 1 model was statistically significant, allowing rejection of the null hypothesis of a flat dose–response curve. Six dose–response models were pre-defined: linear, log-linear, Emax, sigmoid Emax, logistic, and beta model (see Table for model assumptions). Once PoCC was established, the significant models were refitted to the data without assumptions to generate new estimates of the model parameters, and effective doses were predicted from the resulting models.

Results Of 509 randomized patients, 444 (87.2%) completed the 12-week treatment period. PoCC was established, as 5/6 dose–response models were statistically significant for the primary endpoint (Table). The null hypothesis was therefore rejected in favor of a statistically significant benefit of BI 425809 over placebo. Effective doses of 6.85–22.15 mg were predicted from the 5 refitted dose–response models, for an effect size of approximately 0.3 (Table). In the sigmoid Emax and logistic models, the treatment effect tended to reach a plateau at 10 mg. In the linear, log linear, and Emax models, 10–25 mg doses were associated with predicted effect sizes of 1–2 points

improvement in MCCB overall composite T-score at Week 12 vs placebo.
[Table to be inserted by Secretariat]

Conclusion This study established PoCC for the treatment of patients with CIAS with BI 425809 using a MCPMod approach, based on change from baseline in MCCB overall composite T-score at Week 12. Dose selection for future studies will take into account the effective dose range identified using the MCPMod approach, as well as other efficacy and safety data.

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