Brilaroxazine Phase 3 RECOVER Trial in Acute Schizophrenia Supports Efficacy, Safety, and Effects on Neuroinflammation

Poster #T291

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BACKGROUND

Schizophrenia, affecting ~1.1% of the world's population[1], presents as positive, negative, and mood symptoms, cognitive impairment, and immune system abnormalities (neuroinflammation).[2-5] Up to 30% of patients fail current therapies,[6-10] which only manage major symptom domains.[11,12] The suboptimal, broad-spectrum efficacy, intolerable AEs, and drug-induced comorbidities,[13,14] define unmet needs.

Brilaroxazine is a novel multimodal neuromodulator of serotonin and dopamine receptors and a mitigator of multiple inflammatory cytokines.[15-18] Phase 1 and 2 trials, including the Phase 2 REFRESH study, established its unique efficacy, safety, and pharmacokinetic profile.[15-18]

METHODS

Design: This randomized, double-masked, placebo-controlled, multicenter study recruited 411 acute schizophrenia patients to evaluate the efficacy and safety of daily brilaroxazine vs. placebo (15 mg N=140, 50 mg N=134, Placebo N=137) over 28 days. The study was completed in October 2023.

Patients: 18-65 years of age, DSM-5 diagnosed schizophrenia, duration 1-20 years, acute episode of at least moderate baseline Total Positive and Negative Symptom Scores (PANSS) Score 80-120, baseline Clinical Global Impression-Severity (CGI-S) score ≥4.

Endpoints: *Primary*: Baseline change in PANSS vs. placebo at week 4. *Secondary*: PANSS individual symptoms (incl. negative Marder Factors), social cognition and excitement/agitation; Personal and Social Performance (PSP); CGI-S; and treatment-emergent adverse events (TEAEs). vs. placebo. *Exploratory*: Changes in Sexual Functioning Questionnaire (CSFQ)[18] impact on sexual function. Brain-derived neurotrophic factor (BDNF) and Serum Cytokines (Il-8, MIP-1, INF-γ-IP-10 etc.) explored anti-inflammatory effects.

RESULTS

Efficacy: Primary endpoint (PANSS total score) vs. placebo, 50 mg dose achieved a 10.1-point reduction (-23.9 vs. -13.8, p <0.001) (Figure 1); significant and clinically meaningful reductions vs. placebo in Positive (p<0.001), (Figure 2); Agitation/Excitement (p<0.001), (Figure 3); Negative (p=0.003), (Figure 4) and Negative Marder Symptoms (p=0.002), (Figure 5); PANSS Social Cognition (p<0.001), (Figure 6); improvement in Personal and Social Functioning (PSP), (p <0.001), (Figure 7); and Clinical Global Impression- Schizophrenia (CGI-S) (p <0.001), (Figure 8) The 15 mg dose was numerically superior to placebo for all endpoints and significant for social cognition (p=0.024) and PSP (p=0.022) (Figure 6 & 7).

Safety and Tolerability:

Overall TEAEs rates were 34.5% in brilaroxazine 15 mg, 35.5% in 50 mg and 30% in placebo. Common brilaroxazine TEAEs were headache (<6%) and somnolence (≤7.5%), generally transient in nature. No serious adverse events related to brilaroxazine. No incidence of suicidal ideation or suicides. *Metabolic*: No significant change in body weight and blood glucose levels vs placebo (AESI: weight gain 3 (2.1%) in 15 mg, 8 (5.9%) in 50 mg, 4 (2.9%) in placebo). Significant decrease in cholesterol and LDL and increase in HDL vs placebo. *Neuroleptic*: 0.7% Akathisia and 0.7% EPS in 50 mg, none in 15 mg and placebo. *Endocrine*: Significant decrease in prolactin and no change in thyroid levels vs placebo. *Cardiac and GI*: Similar to placebo.

Exploratory: Significant improvement occurred in female sexual function (15 mg p=0.02, 50 mg p=0.03 vs. baseline) (Figure 9). Significant improvement appeared in serum BDNF (p<0.05, 15 mg), (Figure 10) and a decrease in proinflammatory cytokines (IL-8 and MIP-1; both doses, p<0.001) (Figure 11 and 12).

CONCLUSION

Brilaroxazine demonstrates significant efficacy at 50 mg and activity at 15 mg vs. placebo in acute schizophrenia. Patients in this population tolerate both doses well. Exploratory endpoints suggest benefits on sexual function in women and improvements in biomarkers and cytokines associated with neuroinflammation.

Brilaroxazine Demonstrated Strong Efficacy and Was Well Tolerated.

The 50 mg Dose Provided Significant Changes in Primary (Total PANSS) and Secondary Endpoints vs. Placebo; the 15 mg Dose Showed Strong Directional Improvements. Side Effects (Metabolic, Neuroleptic) and Discontinuation Were Similar to Placebo, with Favorable Endocrine Effects.

Figure 1. Primary Endpoint: 10.1-point Reduction in PANSS Total Score vs. Placebo at Week 4, p <0.001 (-23.9 Brilaroxazine 50 mg vs. -13.8 Placebo)

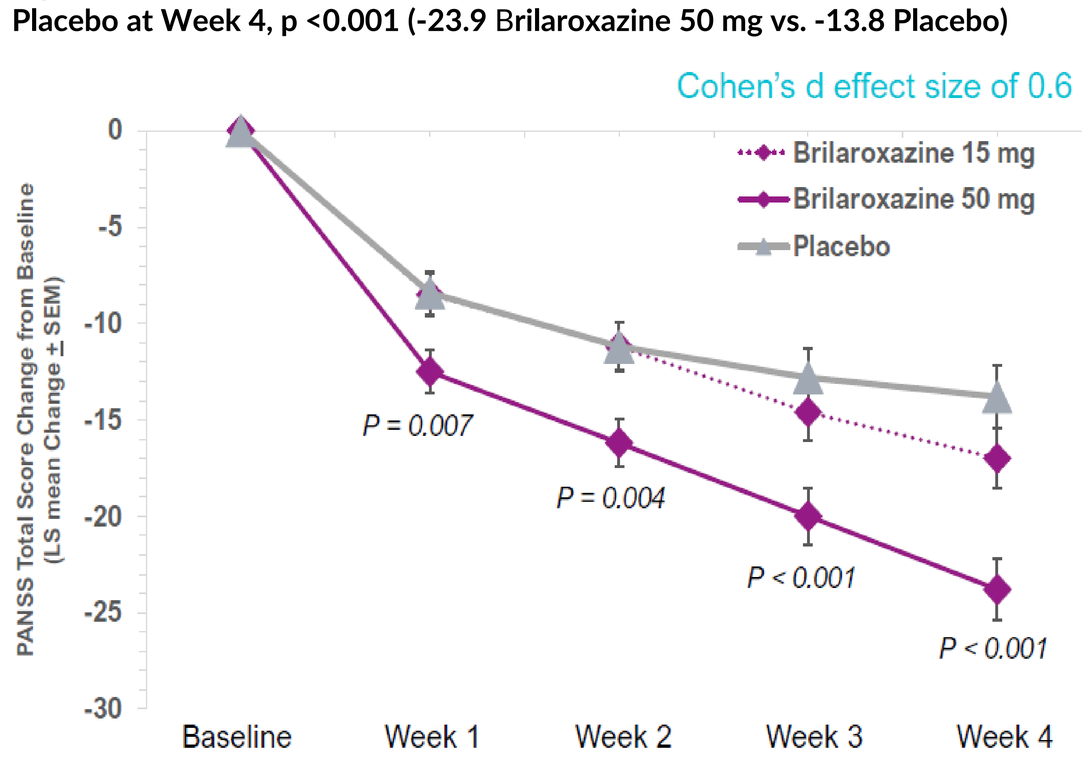


Figure 2. Decrease in Positive Symptoms

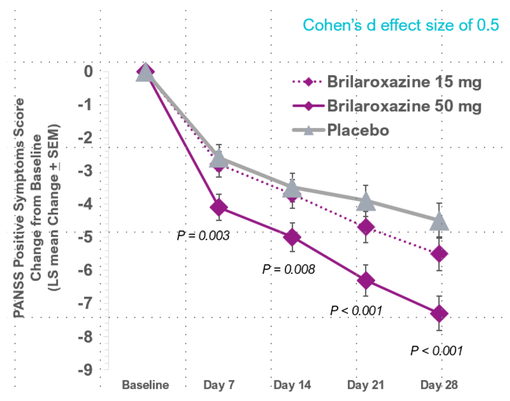


Figure 3. Decrease in Agitation/Excitement Symptoms

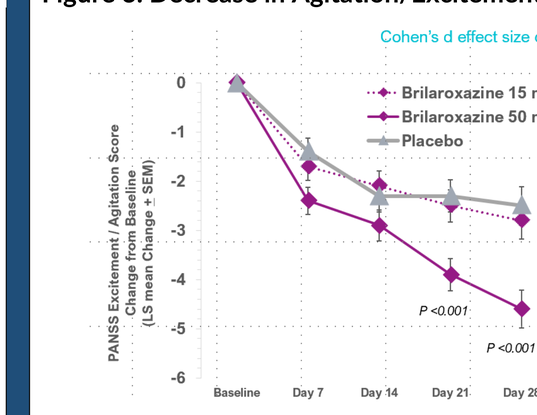


Figure 4. Decrease in Negative Symptoms

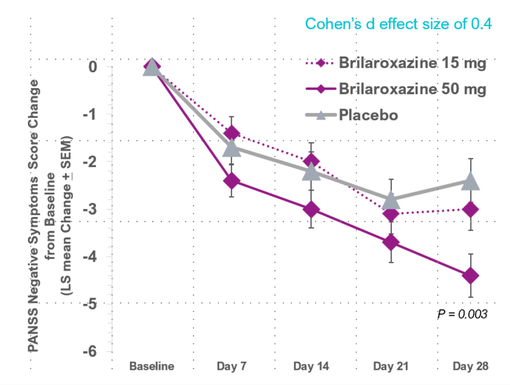


Figure 5. Decrease in Negative Symptoms (Marder Factor)

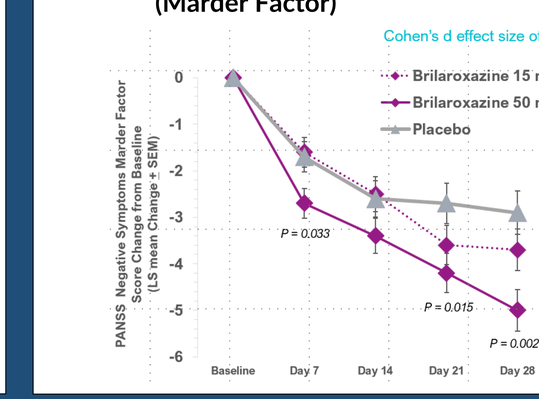


Figure 6. Decrease in Social Cognition Deficits

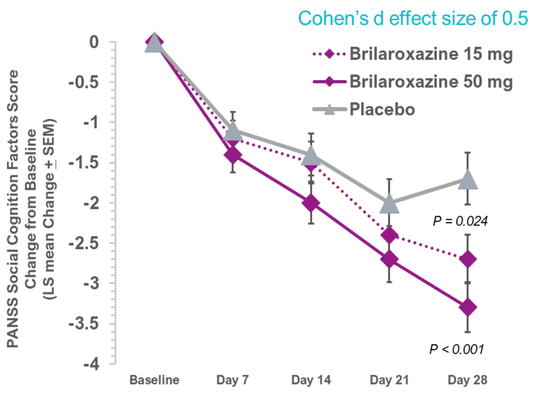


Figure 7. Improvement in PSP Functioning

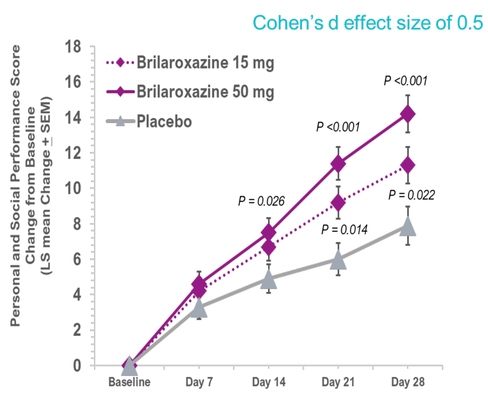


Figure 8. Decrease in CGI-S Score

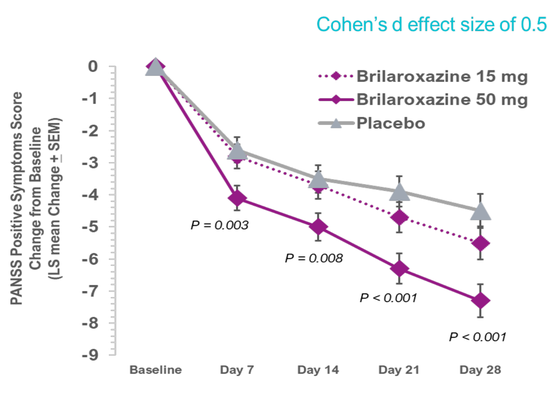


Figure 9. CSFQ Sexual Function in Females

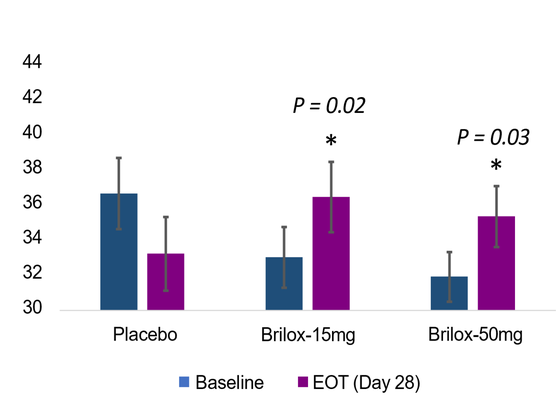


Figure 10. Improvement in BDNF (ng/mL)

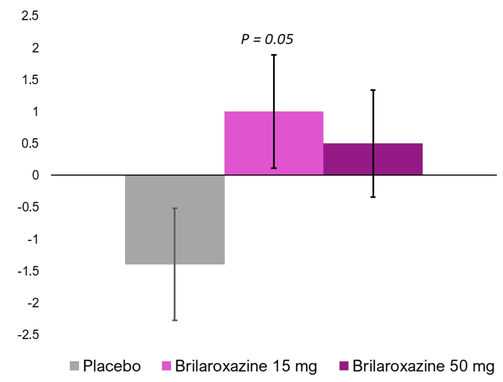


Figure 11. Decrease in IL-8 (ng/mL)

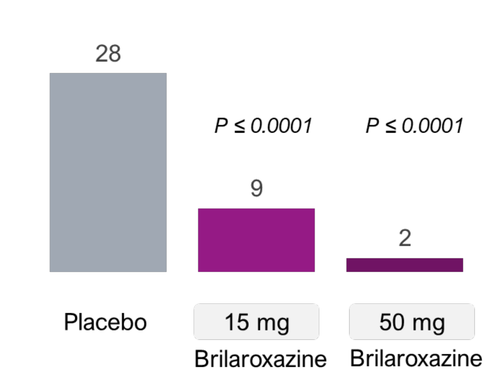
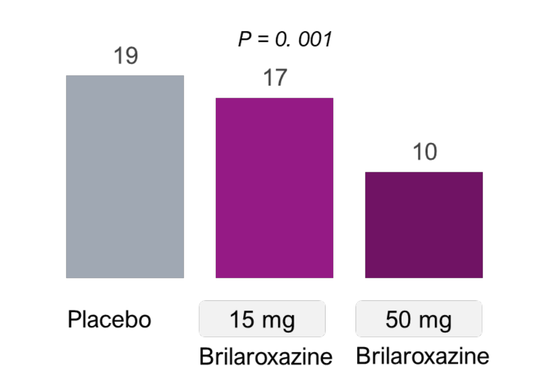


Figure 12. Decrease in MIP-1 (ng/mL)



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