Brilaroxazine Efficacy and Safety in the Phase 3 Recover Trial In Acute Schizophrenia

Poster #: LB-008

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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 (including neuroinflammation).[2-5] Up to 30% of patients fail current therapies,[6-10] which only manage major symptom domains.[11,12] Due to suboptimal, broad-spectrum efficacy, intolerable adverse events, and drug-induced comorbidities,[13,14] these factors define current unmet needs.

Brilaroxazine, a novel multimodal neuromodulator, is a $D_{2/3/4}$ and 5-$HT_{1A/2A}$ partial agonist, a 5-$HT_{2B/7}$ antagonist (binding affinity 5-HT_{2B} > D_2), 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 (Table 3). Distribution: USA 245 (60%), India 140 (34%), Bulgaria 26 (6%) (Table 2).

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 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, 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 (p <0.001), (Figure 7); and CGI-S (p <0.001), (Figure 8) (Table 1). The 15 mg dose was numerically superior to placebo for all endpoints and significant for social cognition (p=0.024) (Figure 6) and PSP (p=0.022) (Figure 7).

Safety and Tolerability:

- Overall treatment-emergent adverse events (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 (SAEs) related to brilaroxazine
- **Metabolic**: No significant change in body weight and blood glucose levels vs 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
- No incidence of suicidal ideation or suicides

Discontinuation:

Discontinuation rate 16% in 50 mg, 19% in 15 mg, and 22% in placebo

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.

Brilaroxazine Demonstrated Strong Efficacy and was Well Tolerated.

The 50 mg dose provided a significant decrease in primary (Total PANSS) and secondary endpoints vs. placebo; the 15 mg dose showed strong directional improvements. Side effects (metabolic, neuroleptic) were similar to placebo with favorable lipid profile and endocrine effects; the discontinuation rate was 6% lower in 50 mg vs. Placebo.

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)

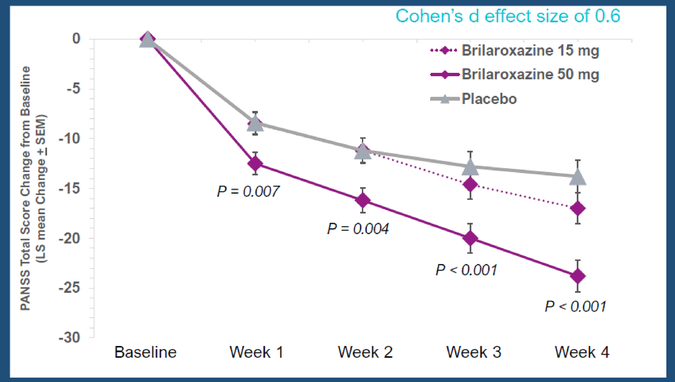


Table 1 Statistically Significant and Clinically Meaningful Improvements Across all Major Symptom Domains with Brilaroxazine 50 mg Vs. Placebo at Week 4

	Brilaroxazine 50 mg vs. Placebo at week 4 Point Reduction / Improvement	*Cohen's d Effect Size*	*P Value*
PANSS Total Score	10.1	*0.6*	*< 0.001*
Positive Symptoms	2.8	*0.5*	*< 0.001*
Negative Symptoms	2.0	*0.4*	*0.003*
Negative Symptoms Marder Factor	2.1	*0.4*	*0.002*
PANSS Social Cognition	1.6	*0.5*	*< 0.001*
PANSS Excitement/Agitation	2.1	*0.5*	*< 0.001*
Personal and Social Performance	6.3	*0.5*	*< 0.001*
CGI-S score	≥1	*0.5*	*< 0.001*

Table 2. Demographics and Baseline Characteristics

	Brilaroxazine 15 mg (n = 140)	Brilaroxazine 50 mg (n = 134)	Placebo (n = 137)
Age (years), Mean (SD)	38.3 (10.88)	39.8 (10.85)	38.4 (10.71)
Male, n (%)	96 (68.6)	96 (71.6)	103 (75.2)
Race, n (%), White	24 (17.1)	26 (19.4)	23 (16.8)
Black	64 (45.7)	59 (44.0)	66 (48.2)
Asian	49 (35.0)	46 (34.3)	44 (32.1)
Other	3 (2.1)	3 (2.2)	4 (2.9)
Baseline PANSS total score, Mean (SD)	97.3 (10.15)	99.1 (9.56)	98.3 (9.48)
Baseline PANSS positive score, Mean (SD)	26.20 (3.58)	26.47 (3.63)	26.53 (3.57)
Baseline PANSS negative score, Mean (SD)	23.58 (4.60)	24.22 (4.60)	24.27 (4.23)
Baseline CGI score, Mean (SD)	4.9 (0.62)	5.0 (0.53)	5.0 (0.56)

Figure 2. Decrease in Positive Symptoms

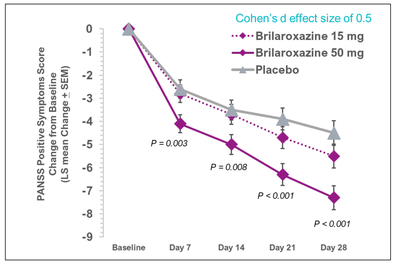


Figure 3. Decrease in Agitation/Excitement Symptoms

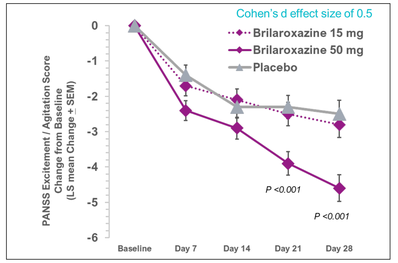


Figure 4. Decrease in Negative Symptoms

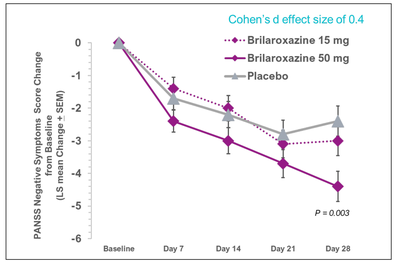


Figure 5. Decrease in Negative Symptoms (Marder Factor)

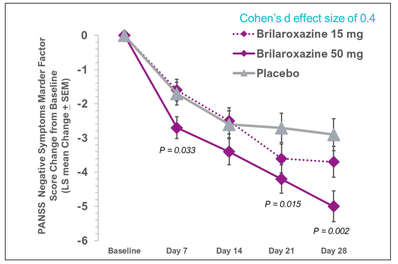


Figure 6. Decrease in Social Cognition Deficits

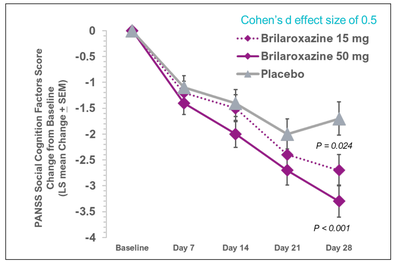


Figure 7. Improvement in Personal & Social Functioning

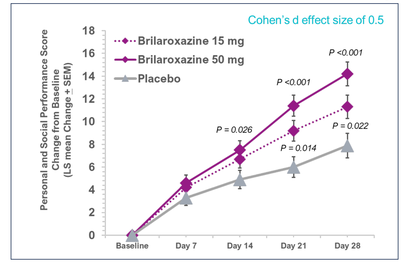
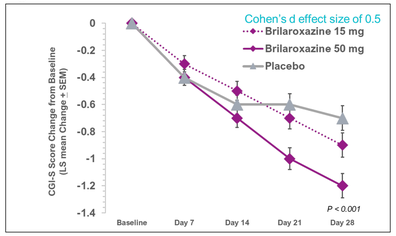


Figure 8. Decrease in CGI-S scores



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