Brilaroxazine Phase 3 RECOVER 52-Week Open-Label Evaluation (OLE) of Efficacy and Safety over 12 Months in Stable Schizophrenia Participants

Poster #155

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BACKGROUND

Schizophrenia impacts ~1.1% of the global population.[1] This complex psychiatric condition presents with positive, negative, and mood symptoms, cognitive impairment, and immune system abnormalities (neuroinflammation).[2-5] Treatment failure with current therapies, which only manage major symptom domains, can occur in up to 30% of patients, especially over time.[6-12] Suboptimal, broad-spectrum efficacy over a long period of treatment, intolerable adverse events, drug-induced comorbidities, and persistency with therapy,[13,14] define unmet needs.

Brilaroxazine (RP5063), a multimodal, serotonin-dopamine neurotransmitter signaling modulator, possesses high affinity (Ki, ≤6nM) and selectivity for key serotonin receptors 5-$HT_{1A/2A/2B/7}$ along with partial agonist functional activities for serotonin 5-$HT_{1A/2A}$ and dopamine $D_{2/4}$ receptors.[15,16] It has reduced proinflammatory cytokines, an underlying disease driver producing neuroinflammation.[17-19]

Clinical experience provides supportive evidence for brilaroxazine's safety and efficacy profile. Phase 1 study in patients with stable schizophrenia established its safety and initial efficacy profile.[20, 21] The Phase 2 REFRESH study (NCT01490086) showcased significant improvements versus placebo for the primary endpoint (Total Positive and Negative Symptom Scores, PANSS), individual PANSS components, and clinical global impression scores (CGI-S).[22] It also finds good tolerability, with insomnia and agitation as the most common treatment-emergent adverse effects, decreases key metabolic and endocrine levels, and low discontinuation rates.[22]

Its multicenter, 28-day, double-blind, randomized, placebo-controlled phase 3 trial (RECOVER, NCT05184335) reinforced prior phase 2 observations. This study demonstrated brilaroxazine's dose-dependent (Figure 1a) and broad-spectrum efficacy at 50 mg (Table 1) and activity at 15 mg compared to placebo for total positive and negative symptom scores (PANSS), multiple symptom domains (PANSS Positive, PANSS Negative, and PANSS Negative Marder), and Clinical Global Impression-Severity (CGI-S) in acute schizophrenia.[23,24] It improved brain-derived neurotrophic factor (BDNF), IL-8, and MIP-1 concentrations and improved sexual functioning in females.[23,24] Brilaroxazine also realized significant treatment improvements from baseline versus placebo in vocal biomarker-positive patients, as compared with vocal biomarker-negative individuals, for primary and secondary endpoints, most notably with negative symptoms at 1,017%.[25] This treatment also showed excellent safety and tolerability in acute schizophrenia patients (Table 2) and low treatment-related discontinuation rates raising the need to pursue a longer-term follow-up evaluation to confirm these observations in stable schizophrenia patients.[23,24]

METHODS FOR OPEN-LABEL LONG-TERM STUDY

Design: To evaluate brilaroxazine's longer-term efficacy, safety, and persistency effects in patients with stable schizophrenia, a 12-month, global, multicenter open-label extension (OLE) followed the initial 4-week double-blind pivotal study. Assessments occurred at baseline, Weeks 2 and 4 in the first month, then every four weeks until Week 52. The first report of completed patients was in December 2024.

Patients: The evaluation involved 435 enrolled participants undergoing treatment at flexible doses (Dose: 139 [15 mg], 155 [30 mg], and 141 [50 mg]). Population selection criteria were 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. The treatment population included 156 participants from the double-blind (rollover) and 279 newly enrolled individuals (de novo).

Endpoints: ***Efficacy***: *Primary* was Total PANSS change from Baseline vs. placebo. *Secondary* included individual PANSS subdomains (including Marder Factors), social cognition, and excitement/agitation; Personal and Social Performance (PSP) and Clinical Global Impressions Scale (CGI-S) changes from baseline vs. placebo. ***Safety***: Treatment-related adverse events (TRAEs), along with monthly laboratory tests and vital sign examinations. ***Persistency:*** Patient adherence and persistency involved tracking participant discontinuation from the trial due to treatment and non-treatment factors.

RESULTS

Efficacy: For all completed patients (N=113), initial findings showed sustained dose-dependent efficacy (Figure 1). The 15, 30, and 50 mg doses showed significant ($p < 0.0001$) reductions in Total PANSS from baseline to Week 52 of -15.2, -18.6, and -20.8 points, respectively. The PANSS total score decreased by more than 30 points in 86.76% of double-blind rollover patients, by more than 40 points in 64.70%, and by more than 50 points in 33.82% (Figure 2). Pooled data (across all doses) showed clinically meaningful, sustained, and statistically significant ($p < 0.0001$) reductions in PANSS Total scores (-18.6), positive symptoms (-5.2), and negative symptoms (-4.5) (Figure 3).

Safety and Tolerability: This evaluation (N = 435) found that 15.2% of participants experienced at least one treatment-related adverse event (TRAE). These were primarily mild (12.2%) or moderate (3%) in severity and transient (Table 3). The most common TRAEs were weight increase (3.2%), insomnia (1.8%), and somnolence (1.6%).

Persistency: The discontinuation rate was 35%, primarily due to consent withdrawal (22%), then lost to follow-up (7%). TREAs accounted for a small portion of discontinuations (1.6%) (Table 4.).

CONCLUSION

Overall, findings from the brilaroxazine phase 3 OLE part reinforce the initial safety and efficacy results from the double-blind part of the phase 3 trial (RECOVER), emphasizing a dose-dependent effect. Furthermore, they highlight the sustainability of brilaroxazine's significant, broad-spectrum efficacy on Total PANSS, along with Positive and Negative components, and that patients tolerated this treatment well, as evidenced by low TREAs and high adherence to therapy. collectively, these findings strengthen the overall efficacy, safety, and treatment adherence profile of brilaroxazine.

Brilaroxazine Remained Efficacious Across a Broad Span of Symptoms and Well Tolerated– While Displaying Strong Treatment Adherence– Over the 52-week Open-Label Evaluation Period

Sustained Dose-dependent Efficacy. Common TREAs Were Weight Increase, Insomnia, and Somnolence. Drug-related Discontinuation Was 1.6%.

Figure 1. Dose-Dependent Change in the Primary Endpoint PANSS Total Scores in a) the 4-week, double-blind pivotal trial (n=411, p<0.001 [50 mg]), and b) the 52-week OLE (N=113, p <0.0001).

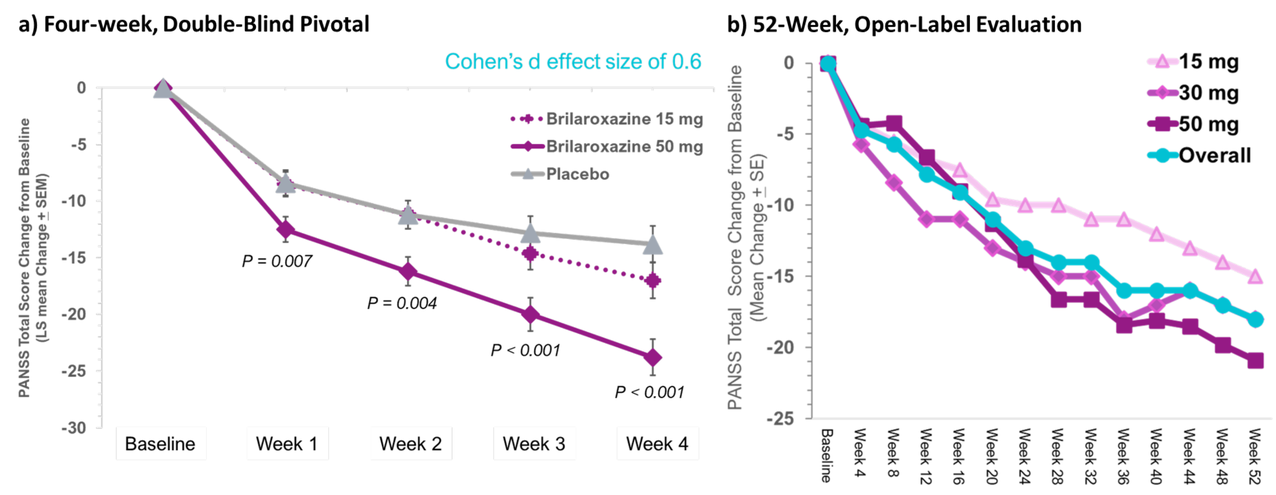

Table 1. Improvements Across All Major Symptom Domains in the 4-Week, Double-Blind Pivotal Trial.

	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*

Figure 2. OLE PANSS Total Score Percent Decrease : >30%, >40%, and >50%

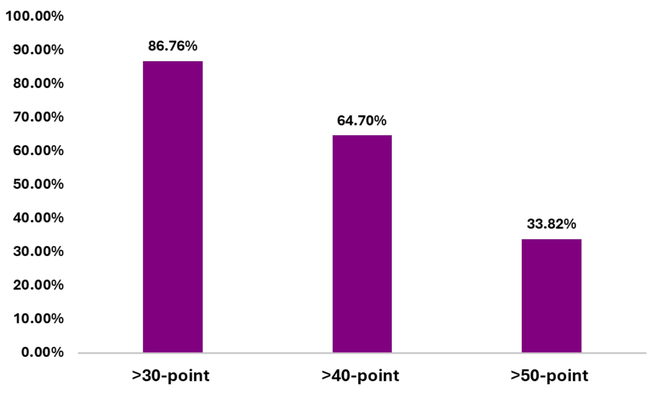

Figure 3. OLE Pooled Data Findings for Baseline and Week-52 for PANSS Total, Positive, and Negative.

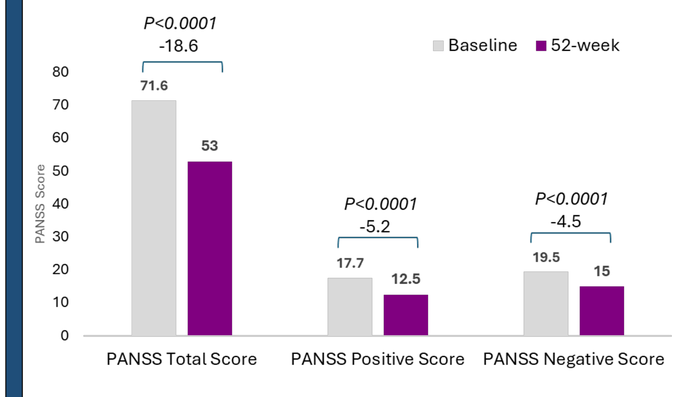

Table 2. Safety and Tolerability in the 4-week Double-blind Pivotal Trial (n=411)

Variables	Brilaroxazine 15 mg (N=140)	Brilaroxazine 50 mg (N=134)	Placebo (N=137)
Any Treatment Emergent Adverse Event (TEAE)	104 (34.5%)	107 (35.5%)	90 (29.9%)
Discontinuation, n (%)	26 (18.6%)	22 (16.4%)	30 (21.9%)
TEAE occurring in >5% participants			
Somnolence	4 (2.9%)	10 (7.5%)	3 (2.2%)
Headache	8 (5.7%)	7 (5.2%)	3 (2.2%)
Metabolic Changes (weight and lipids), TEAE			
Body Weight Change in kg, Least Square Mean (SE)	1.91 (0.30)	2.41 (0.30)	0.82 (0.30)
≥7% Increase in Body Weight, n (%)	3 (2.1)	8 (5.9)	4 (2.9)
Cholesterol change in mg/dl, Mean (SD)	-2.4 (27.99)	-4.73 (26.13)	3.65 (28.47)
LDL change in mg/dL, Mean (SD)	-4.38 (22.63)	-5.71 (22.06)	4.07 (24.07)
HDL change in mg/dL, Mean (SD)	1.54 (10.46)	0.48 (13.27)	-2.16 (10.18)
Extrapyramidal Symptoms, TEAE			
Barnes Akathisia Rating Scale Score, Mean (SD)	0.0 (0.13)	0.0 (0.19)	0.1 (0.35)
Abnormal Involuntary Movement Scale Score, Mean (SD)	-0.0 (0.41)	-0.0 (0.28)	0.0 (0.48)
Simpson-Angus Scale Score, Mean (SD)	0.1 (0.42)	0.2 (0.48)	0.3 (0.71)

Table3. Safety and Tolerability in the OLE (n=113)

Category	Details
TRAEs reported	15.2% reported at least one TRAE
Severity of TRAEs	Mild (12.2%), Moderate (3%), Transient in nature
Common TRAEs (>1%)	Weight increase (3.2%), Insomnia (1.8%), Somnolence (1.6%)
Movement Disorder Scales	No clinically meaningful changes observed
Serious Adverse Events (SAEs)	No drug-related SAEs; 3 SAEs reported, none brilaroxazine-related

Table 4. Discontinuations and Adherence in the OLE (n=113)

Discontinuation Category	Percentage
Overall rate	35%
Withdrawal of consent-related	22%
Lost to Follow-Up-related	7%
TRAE-related	1.6%

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