Poster # 32

Brilaroxazine Treatment Effect on Negative Symptoms in Schizophrenia: RECOVER Trial in Acute and Stable Patients Over 1 Year

Authors: Laxminarayan Bhat, Seema R. Bhat, Wasim Khan, Arulprakash Ramakrishnan, and Simeen Khan *(Reviva Pharmaceuticals, Cupertino, CA, USA)*

Disclosures: L Bhat, SR Bhat, W Khan, A Ramakrishnan, and S Khan are Reviva Pharmaceuticals Employees

https://rb.gy/nxi9og

Key Findings

1. **RECOVER Trial:** Brilaroxazine 50 mg significantly improved negative symptoms (PANSS and Marder Negative factors), with effect sizes at the high end of historical benchmarks
2. **Open-label Extension:** Benefits were **durable**, with sustained improvements over 52 weeks (up to −10.5 points in rollover patients).
3. **Vocal Biomarker-Positive Subgroup:** Showed a **markedly greater response**, with over tenfold larger effects on negative symptoms than vocal biomarker-negative patients.
4. **Treatment Adherence:** Compared to historical data of approved antipsychotics, brilaroxazine treatment discontinuation rates were **~50% lower** in the **double-blind trial** in acute patients (16% in 50mg vs 22% in placebo) and in the **open-label extension trial** in stable patients (35%)

Introduction

Schizophrenia affects approximately 1% of the population and remains a leading cause of disability worldwide.[1,2] Negative symptoms—including avolition, anhedonia, blunted affect, and social withdrawal—represent the most significant unmet need in treatment. They drive functional impairment and disability, yet current antipsychotics provide modest and inconsistent relief.[1] While antipsychotics effectively reduce positive symptoms, negative symptoms persist in many patients and are strongly correlated with poor functional outcomes.[3] Meta-analyses confirm the limited efficacy of risperidone, olanzapine, quetiapine, and aripiprazole,[4] while cariprazine shows moderate benefit but lacks durability.[5]

Brilaroxazine (RP5063) is a multimodal serotonin–dopamine neuromodulator with partial agonist activity at 5-$HT_{1A/2A}$ and $D_{2/4}$ receptors and effects on neuroinflammation.[3-14] The pivotal Phase 3 RECOVER trial plus its 52-week open-label extension (OLE) showed efficacy for the primary endpoint total Positive and Negative Symptom Scores (PANSS). This study also provided critical insight into brilaroxazine's impact on negative symptoms.[15-16] Analysis involving vocal biomarker (VBM) effects in the RECOVER trial showed significant effects in patients who were VBM-positive.[17]

Objective

This analysis aimed to address the specific question regarding the brilaroxazine's short-term (28-day) and persistent (52-week) effectiveness on PANSS Negative symptoms in acute patients and stable patients with schizophrenia, respectively.

Methods

RECOVER: This Phase 3 trial involved a 28-day, randomized, double-blind, placebo-controlled Phase 3 study that enrolled 411 patients experiencing an acute episode of schizophrenia. Investigators randomized participants to receive brilaroxazine 15 mg, 50 mg, or placebo, and conducted follow-up assessments weekly for four weeks to Day 28. The primary endpoint was PANSS total score. Secondary endpoints assessed PANSS subdomains, CGI-S, PSP, safety, and adherence.

Open-label Extension (OLE): This investigation evaluated long-term brilaroxazine treatment. Investigators enrolled 446 participants, including 156 rollover patients from RECOVER and 290 de novo participants. They treated patients with flexible dosing of 15, 30, or 50 mg brilaroxazine and followed them from Week 4 through Week 52. Assessments included PANSS total and domain scores, CGI-S, PSP, safety, and adherence.

Speech Latency Biomarker: Both studies captured voice recordings during psychiatric interviews and classified patients as vocal biomarker–positive (VBM-Positive) if latency shortened, indicating improvement, or vocal biomarker–negative (VBM-Negative) if latency increased, indicating worsening. The RECOVER dataset included 2,590 recordings from 408 participants,

Analyses: This evaluation focused on Negative Symptoms and the Marder factor. Investigators applied a mixed model for repeated measures (MMRM) with the treatment × time interaction as the primary test of efficacy. They estimated effect sizes with Cohen's d and evaluated treatment response for all efficacy endpoints in VBM-Positive versus VBM-Negative patients, with a particular emphasis on negative symptoms.

Results

Phase 3 RECOVER Double-blind Trial in Acute Schizophrenia Patients (4 Weeks, N=411): In the 28-day Phase 3 RECOVER trial, brilaroxazine 50mg dose group improved negative symptoms, with −2.0 points on the PANSS Negative subscale (p=0.003; d=0.4; Figure 1) and −2.1 points on the Marder Negative factor (p=0.002; d≈0.4; Figure 2) net of placebo. In the vocal biomarker–positive (VBM-Positive) subgroup, treatment effects were amplified more than tenfold compared with biomarker-negative patients, with consistent advantages across both PANSS Negative domain (Figure 3).

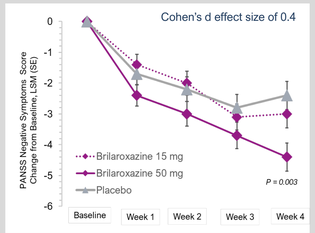

Figure 1. Decrease in Negative Symptoms Over 28 Days

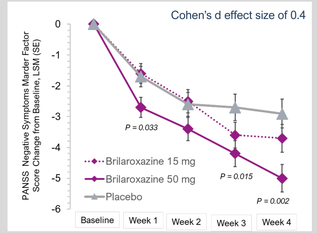

Figure 2. Decrease in Negative Symptoms Marder Factors Over 28 Days

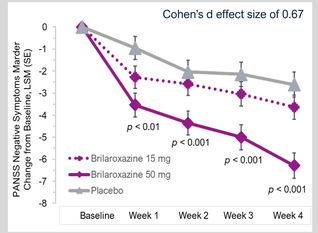

Figure 3. Decrease in Negative Symptoms Over 28 Days (VMB-Positive)

Acute Schizophrenia Patients Rollover from Double-blind Trial (4 weeks) to Open-label Extension Trial (52 Weeks): Rollover patients who completed 52 weeks of treatment in the brilaroxazine 50 mg dose group (N=23) showed -49.7 points decrease on PANSS Total score (Figure 4), -10.7 points on PANSS Negative Symptom (Figure 5), and -10.9 on PANSS Negative Symptom Marder Factor (Figure 6) from the baseline. The rollover patients who completed 52 weeks of treatment in brilaroxazine 15 mg dose group (N=27) also showed similar improvements with -46.7 points decrease on PANSS Total score, -10.4 points on PANSS Negative Symptom, and -10.1 on PANSS Negative Symptom Marder Factor from the baseline.

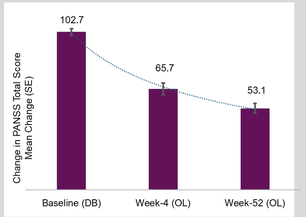

Figure 4. Decrease in PANSS Total Score in DB Rollover to OLE over 1 Year

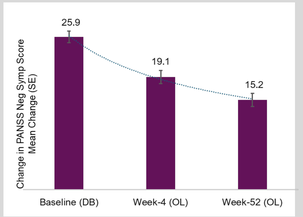

Figure 5. Decrease in PANSS Negative Symptom Score in DB Rollover to OLE over 1 Year

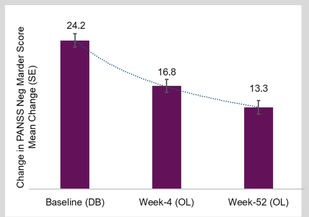

Figure 6. Decrease in PANSS Marder Negative Factor Score in DB Rollover to OLE over 1 Year

Discussion

In these studies, brilaroxazine demonstrated robust and durable efficacy for negative symptoms, addressing a long-standing therapeutic gap in schizophrenia. In the RECOVER study, brilaroxazine displayed significant and clinically meaningful improvements on both PANSS Negative Symptom and PANSS Negative Marder Factor scores, with effect sizes greater than most historical comparators. The OLE confirmed durability across 52 weeks, a rarity in negative-symptom pharmacotherapy. These findings confirm that brilaroxazine sustains and deepens Negative symptom and Negative Marder symptom improvements across a full year. Brilaroxazine's consistency across acute and maintenance phases distinguishes it in this therapeutic space.

Phase 3 RECOVER Open-label Extension Trial in Clinically Stable Schizophrenia Patients (52 Weeks, N=446): Patients in all three dose groups of brilaroxazine (15, 30, and 50mg) showed progressive and durable improvements. PANSS Negative symptoms scores decreased by −3.5 to 4.9 points (74-81%) from baseline (Figure 7). Similarly, PANSS Negative symptom Marder Factor scores decreased by −3.4 to 4.8 points (70-79%) from baseline (Figure 8).

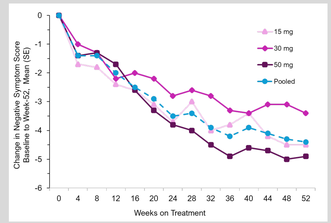

Figure 7. Decrease in PANSS Negative Symptom Score in OLE over 52 weeks (1 Year)

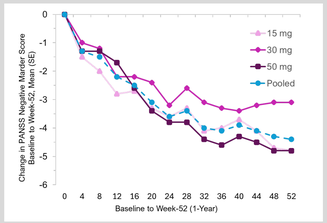

Figure 8. Decrease in PANSS Marder Negative Factor Score in OLE over 52 weeks (1 Year)

Conclusion

Brilaroxazine significantly improves negative symptoms in schizophrenia across both acute (28-day) and clinically stable long-term (52-week) treatment phases. Its effect sizes exceed historical comparators and sustained improvement over one-year establish a differentiated long-term profile. The addition of a speech latency biomarker in the acute study enriches treatment response, offering a pathway to targeted interventions in a domain of persistent unmet need. The durability of response over 52 weeks and the amplification observed in biomarker-positive patients in the acute study support a differentiated role for brilaroxazine in schizophrenia management. These findings advance the field toward precision psychiatry and provide a strong rationale for brilaroxazine as a potential next-generation therapy for negative symptoms.

References

1. Kahn RS, et al. *Nature Reviews Disease Primers*. 2015.
2. Goff DC. *World Psychiatry*. 2021
3. Marder SR & Galderisi S. World Psychiatry, 2023.
4. Leucht S, et al. *The Lancet*. 2013.
5. Marder SR et al. *Psychiatry Research*.
6. Bhat L, et al., *European journal of Pharmacology*. 2017a.
7. Bhat L, et al., *European journal of Pharmacology*. 2017a.
8. Bhat, et al. *Journal of Neurology and Neuromedicine*. 2018.
9. Bhat, et al. *Medical Research Archives*. 2023.
10. Cantillon M, et al., *Clinical and Translational Science*. 2018a.
11. Cantillon M, et al., *Clinical and Translational Science*. 2018b.
12. Koester LS, et al. *Expert Opin. Emerg Drugs*. 2014.
13. Rajagopal L, et al.*Behavioural Brain Research*. 2017.
14. Tsapakis EM, et al., *Brain Sciences*. 2023.
15. Bhat, L et al. *Schizophrenia International Research Society Conf*.. 2024.
16. Bhat, L et al. *Schizophrenia International Research Society Conf*.. 2024.
17. Cohen A, et al. *CNS Summit*. 2024
18. Correll CU & Schooler NR. *CNS Drugs*. 2020.