Brilaroxazine treatment effects on BDNF and inflammatory cytokines in schizophrenia: RECOVER trial in acute and stable patients over 1 year

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Key Findings

1. **Randomized Trial in Acute Schizophrenia:** Brilaroxazine increased BDNF and reduced IL-8, TNF-α, IFNγ-IP and MIP-1 levels compared placebo over 28 days /1 month in RECOVER.
2. **Open-label Trial in Stable Schizophrenia:** Brilaroxazine increased BDNF and reduced IL-6, IL-10, IFN-γ, IFN-γ-IP, TNF-α, MIP-1 and MCP-1 from baseline over 52 weeks / 1 year.
3. BDNF and inflammatory cytokine changes align with positive clinical improvements observed in measures for efficacy and side effects both in acute and stable schizophrenia.
4. Findings of reduction in proinflammatory cytokines are consistent with preclinical anti-inflammatory activity of brilaroxazine in PAH, IPF, and psoriasis models.
5. Brilaroxazine engages in a dual mechanism—neurotransmission modulation and neuroinflammation reduction— as evidenced via these cytokine and BDNF changes.

Introduction

Schizophrenia involves dysregulation across dopaminergic/ serotonergic systems and immune pathways, with reduced BDNF and elevated IL-6, IL-8, TNF-α, IFN-γ, and MIP-1 associated with symptom burden, cognition, and outcomes.[1-4]

Brilaroxazine (RP5063) is a multimodal serotonin–dopamine neuromodulator with partial agonist activity at 5-$HT_{1A/2A}$ and $D_{2/4}$ and antagonist activity for 5-$HT_{2B/7}$ receptors and effects on neuroinflammation.[5-14] Phase 1 and the Phase 2 REFRESH study established safety and early efficacy signals.[9-11] The pivotal Phase 3 RECOVER trial and its 52-week open-label extension (OLE) in schizophrenia patients showed significant and sustained efficacy on the primary endpoint PANSS Total and multiple secondary endpoints.

Preclinical studies also demonstrate anti-inflammatory activity: in PAH models, brilaroxazine reduced TNF-α, IL-1β, IL-6.[5,6]; in IPF, it attenuated fibrosis and cytokines,[8,] and in psoriasis, it reduced Ki-67, TGF-β, and inflammatory cytokines.[15]

Objective

Evaluate brilaroxazine's effects on proinflammatory cytokines, chemokines, and BDNF in schizophrenia during acute treatment (RECOVER, 28 days) and sustained therapy (OLE, 52 weeks).

Methods

RECOVER: This 28-day, randomized, double-blind, placebo-controlled Phase 3 study in acute schizophrenia (N=411) compared brilaroxazine 15 mg or 50 mg with placebo. An exploratory biomarker substudy quantified from baseline to Day 28 change in IL-6, IL-8, IL-10, IFN-γ, TNF-α, MIP-1, IP-10, and BDNF, and compared dose arms with placebo.

OLE: The OLE enrolled 446 patients (156 rollover, 290 de novo) for 52 weeks of open-label brilaroxazine (flexible 15/30/50 mg). The study assessed biomarkers (IL-6, IL-8, IL-10, IFN-γ, TNF-α, MIP-1, IP-10, BDNF) at baseline and Week 52; analyses focused on change from baseline in the pooled-dose population.

Analysis of exploratory endpoints used Analysis of Covariance (ANCOVA) for continuous outcomes and logistic regression for categorical outcomes. Two-sided p < .05 defined statistical significance.

Results: RECOVER

Over 28 days, brilaroxazine reduced pro-inflammatory cytokines and enhanced neurotrophic support versus placebo. BDNF rose at 15 mg (Δ≈ +1 ng/mL; p = 0.02) and trended upward at 50 mg (Figure 1). In brilaroxazine 50 mg compared to placebo, IL-8 fell sharply from 29.13 to 4.25 ng/L, TNF-α from 0.33 to 0.13 ng/L, IFN-γ-IP from 27.64 to -8.58 ng/L and MIP-1 declined from 19.36 to 10.47 ng/L (Figure 2). Consistent decrease in multiple proinflammatory cytokines in brilaroxazine treatment group compared to placebo indicate mechanism driven an anti-inflammatory effect. These biomarker changes paralleled improvements in efficacy across multiple domains, underscoring brilaroxazine's multimodal neuro-immune mechanism.

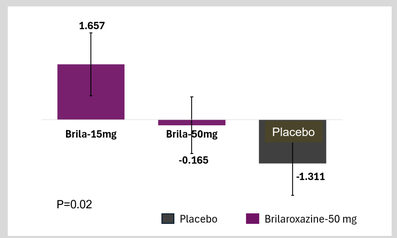

Figure 1. RECOVER Trial – BDNF: Mean (±SE) change from baseline to Day 28 by treatment arm. A significant increase was observed with brilaroxazine 15 mg (p = 0.02) versus placebo; a directional increase was noted at 50 mg.

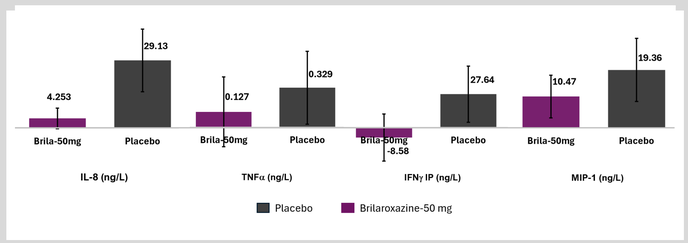

Figure 2. RECOVER Trial – Cytokines and Chemokines: Mean (±SE) change from baseline to Day 28 by treatment arm. Brilaroxazine 50 mg produced marked reductions in IL-8, TNF-α, IFN-γ-IP and MIP-1 versus placebo. Inset panels also show directional decreases in IL-6 and IFN-γ, consistent with an anti-inflammatory profile.

Results: OLE

In the OLE, brilaroxazine sustained and extended biomarker effects over 52 weeks (pooled doses 15, 30, 50 mg). BDNF increased by +1.83 µg/L (p = .081), indicating durable neurotrophic support. Pro-inflammatory cytokines declined from baseline (ng/L): IL-6 (−0.71), IL-8 (−0.16), IL-10 (-1.43; P=0.0001), TNF-α (−0.72; P=0.01), IFN-γ (2.61), IFN-γ-IP (37.82; P= <0.01), MIP-1 (−14.58; P=0.03) and MCP-1 (-9.05). These sustained molecular effects paralleled continued clinical improvement across the open-label extension period, reinforcing brilaroxazine's long-term anti-inflammatory and neurotrophic profile.

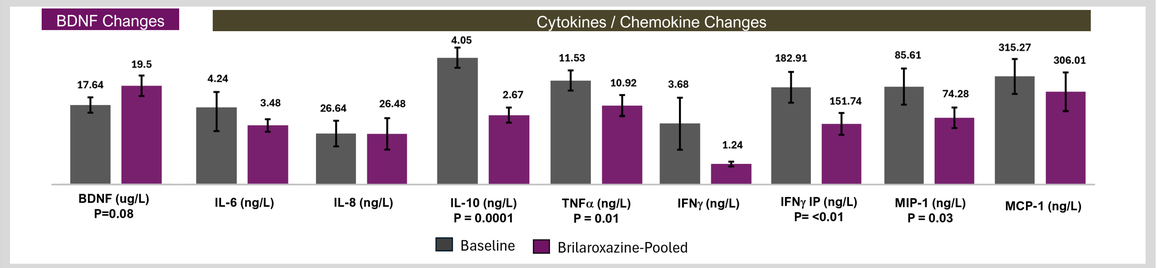

Figure 3. RECOVER OLE – BDNF and Cytokines/Chemokines: Mean (±SE) change from baseline to Week 52 (pooled dose). BDNF increased (p = 0.08), indicating sustained neurotrophic support. Pro-inflammatory mediators declined over time: IL-6, IL-8, IL-10 (p = 0.0001), TNF-α (p = 0.01), IFN-γ, IFN-γ -IP (P = <0.01), MIP-1 (p = 0.03) and MCP-1.

Discussion

These clinical biomarker findings demonstrate that brilaroxazine attenuates peripheral inflammatory activity and enhances neurotrophic support in schizophrenia. In the RECOVER trial, early reductions in IL-8, TNF-α, IFN-γ and MIP-1, alongside increased BDNF, emerged within 28 days. In the open-label extension (OLE), these effects deepened and broadened, with significant, durable decreases in IL-6, IL-8, IL-10, TNF-α, IFN-γ, IFN-γ-IP, and MIP-1, and a sustained rise in BDNF over 52 weeks. This pattern mirrors evidence linking chronic neuroinflammation and reduced BDNF to symptom persistence and cognitive dysfunction in schizophrenia.[1–4] The integrated modulation of cytokines, chemokines, and neurotrophic signaling provides a mechanistic rationale for the enduring clinical benefits observed with brilaroxazine, supporting its potential to target both inflammatory and neuroplastic pathways underlying disease progression.

Translational evidence strengthens this interpretation. In PAH models, brilaroxazine suppressed TNF-α, IL-1β, IL-6 and attenuated vascular remodeling.[5-7] In IPF, it reduced fibrosis and inflammatory cytokines.[7] In psoriasis, it decreased proliferative/ inflammatory markers.[15] The cross-model consistency suggests that brilaroxazine's serotonergic–dopaminergic modulation intersects immune pathways to yield clinically meaningful anti-inflammatory signatures in patients.

Conclusion

Brilaroxazine significantly reduced pro-inflammatory cytokines and increased BDNF across both the 28-day RECOVER trial and the 52-week open-label extension (OLE). These sustained biomarker improvements parallel clinical benefits and align with preclinical evidence of anti-inflammatory activity. Together, the findings support a dual-mechanism model—combining modulation of neurotransmission and attenuation of neuroinflammation—as a biologically grounded basis for improved outcomes in schizophrenia.

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