



REVIVA PHARMACEUTICALS HOLDINGS, INC. (NASDAQ: RVPH)

Corporate Presentation, March 2024



Forward-Looking Statements

This presentation contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's 1-year Phase 3 open-label extension (OLE) trial evaluating the long-term safety and tolerability of brilaroxazine, the Company's registrational Phase 3 RECOVER-2 trial, the Company's expectations regarding the anticipated clinical profile of its product candidates, including statements regarding anticipated efficacy or safety profile, and those relating to the Company's expectations, intentions or beliefs regarding matters including product development and clinical trial plans, clinical and regulatory timelines, planned or intended additional trials and the timing thereof, planned or intended regulatory submissions and the timing thereof, trial results, market opportunity, ability to raise sufficient funding, competitive position, possible or assumed future results of operations, business strategies, potential growth, financing, partnership, expansion and other opportunities and other statements that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions. These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or the Company's financial performance and involve known and unknown risks, uncertainties, and other factors, on the Company's operations, clinical development and clinical trial plans and timelines, which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's most recent Annual Report on Form 10-K for the fiscal year ended December 31, 2022, and the Company's other filings from time to time with the Securities and Exchange Commission (the "SEC"). Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this presentation. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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This presentation also contains estimates and other statistical data made by independent parties and by the Company relating to market size and growth and other data about the Company's industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates.

Late-stage Clinical Program with Differentiated Profile in Schizophrenia

Brilaroxazine – A once-daily, serotonin-dopamine signaling modulator with potential to reduce neuroinflammation

De-risked Program with Multiple Successful Trials

Positive Phase 3 trial in N = 411 schizophrenia patients

Positive Phase 2 trial in N = 234 schizophrenia patients

Completed most non-clinical activities supporting NDA

Compelling Topline Phase 3 RECOVER-1 Data

Primary Endpoint: 10.1-point reduction in PANSS total score in brilaroxazine 50 mg vs placebo

Statistically significant results on all secondary endpoints including reduction in positive symptoms, negative symptoms, and social cognition deficits

Near-term Registration Pathway

RECOVER-2; Registrational Ph3

- Expected initiation in Q1 2024
- Topline readout in Q2 2025

Long-term clinical safety trial topline in Q4 2024

Potential NDA filing in Q3 2025

Extensive Clinical Development Pipeline

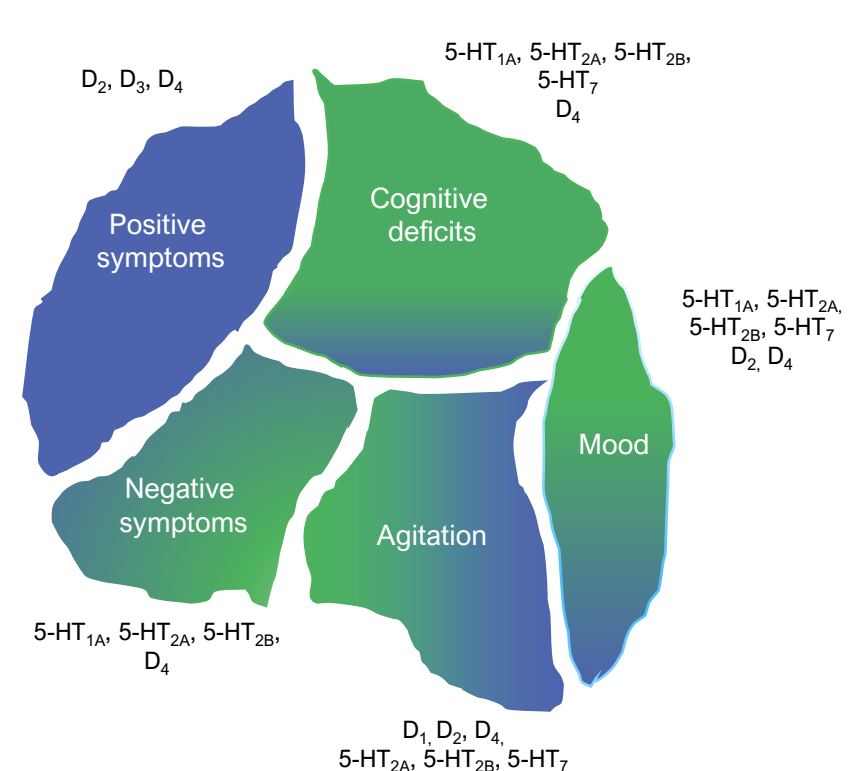
			Discovery	Preclinical	Phase I	Phase II	Phase III	Est. Market Opportunity (\$B)
Brilaroxazine – Serotonin/ dopamine modulator (NCE)	Neuropsychiatric	Schizophrenia						\$12.6 ⁽¹⁾
		Bipolar Disorder						\$6.4 ⁽²⁾
		Major Depressive Disorder						\$16.8 ⁽³⁾
		Attention Deficit Hyperactivity Disorder						\$32.1 ⁽⁴⁾
	Inflammatory	Pulmonary Arterial Hypertension						\$10.9 ⁽⁵⁾
		Idiopathic Pulmonary Fibrosis						\$7.5 ⁽⁶⁾
		Psoriasis (topical gel)						\$57.7 ⁽⁷⁾
RP1208 – Triple reuptake inhibitor (NCE)		Depression						\$16.8 ⁽³⁾
		Obesity						\$77 ⁽⁸⁾

*Opportunity to expand into other indications including Parkinson's Psychosis and Alzheimer's (Psychosis/agitation)

Schizophrenia: Common Psychiatric Condition With Multiple Symptom Domains

Primarily driven by dysfunctional serotonin and dopamine signaling

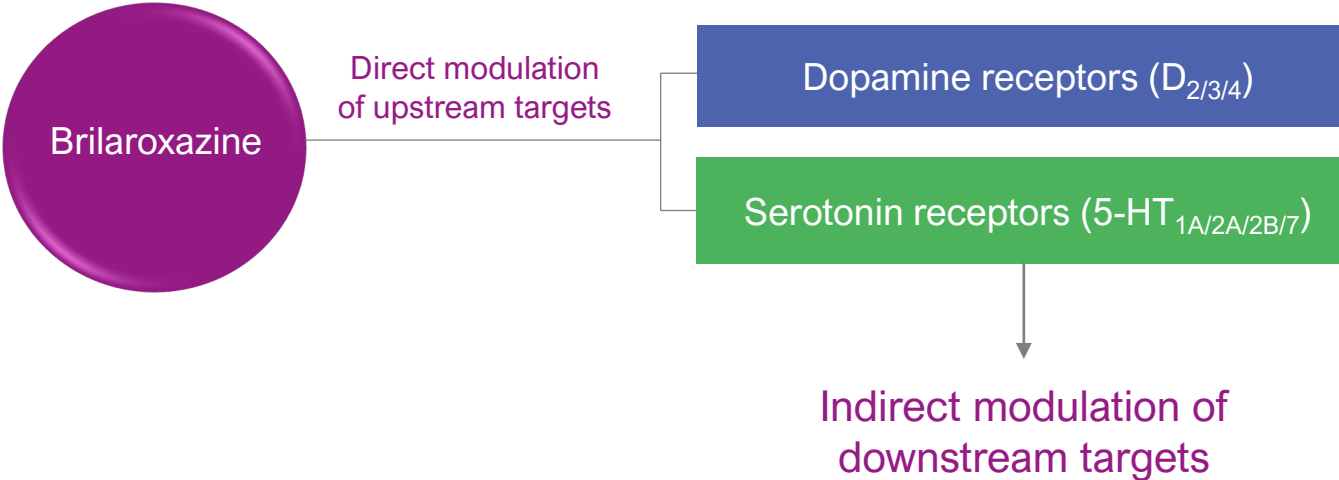
- Affects ~1.1% of the world's population
 - ~ 24 million people globally
 - ~ 6.2 million people in 7 major markets (USA, EU-4, UK, Japan) with highest in USA
- Leading cause of disability worldwide, with onset in late-teens and early-adulthood
- Requires lifelong treatment
- ~30% of patients are treatment refractory
- Neuroinflammation is implicated as a major contributing factor to schizophrenia



Source: Delveinsight Market Research 2023; <https://www.mentalhelp.net/schizophrenia/statistics/>; <https://www.who.int/news-room/fact-sheets/detail/mental-disorders>; <https://fherehab.com/schizophrenia/statistics>; <https://www.nimh.nih.gov/health/statistics/schizophrenia>; Kane JM et al. J Clin Psychology 2019, 80(2):18com12123..

Brilaroxazine: Novel Serotonin Dopamine Signaling Modulator

Multi-faceted direct and indirect activities on critical pathways implicated in schizophrenia



Brilaroxazine Receptor Activities		
High (K_i , nM)* ($5-HT_{2B} > D_2$)	Dopamine D_2	0.4
	Dopamine D_3	3.7
	Dopamine D_4	6
	Serotonin $5-HT_{1A}$	1.5
	Serotonin $5-HT_{2A}$	2.5
	Serotonin $5-HT_{2B}$	0.19
	Serotonin $5-HT_7$	2.7
Moderate (K_i , nM)	Nicotine $\alpha_4\beta_2$	36.3
	Serotonin $5-HT_6$	51
Weak or no significant activity	No significant activities at therapeutic dose for off-targets $5-HT_{2C}$, $\alpha_{1,2}$, and M_{1-4} implicated in cardiometabolic, metabolic, or GI side effects	

Inflammatory cytokines

Implicated in neuroinflammation

Nicotinic receptors

Implicated in positive symptoms and cognition

NMDA/Glycine receptors

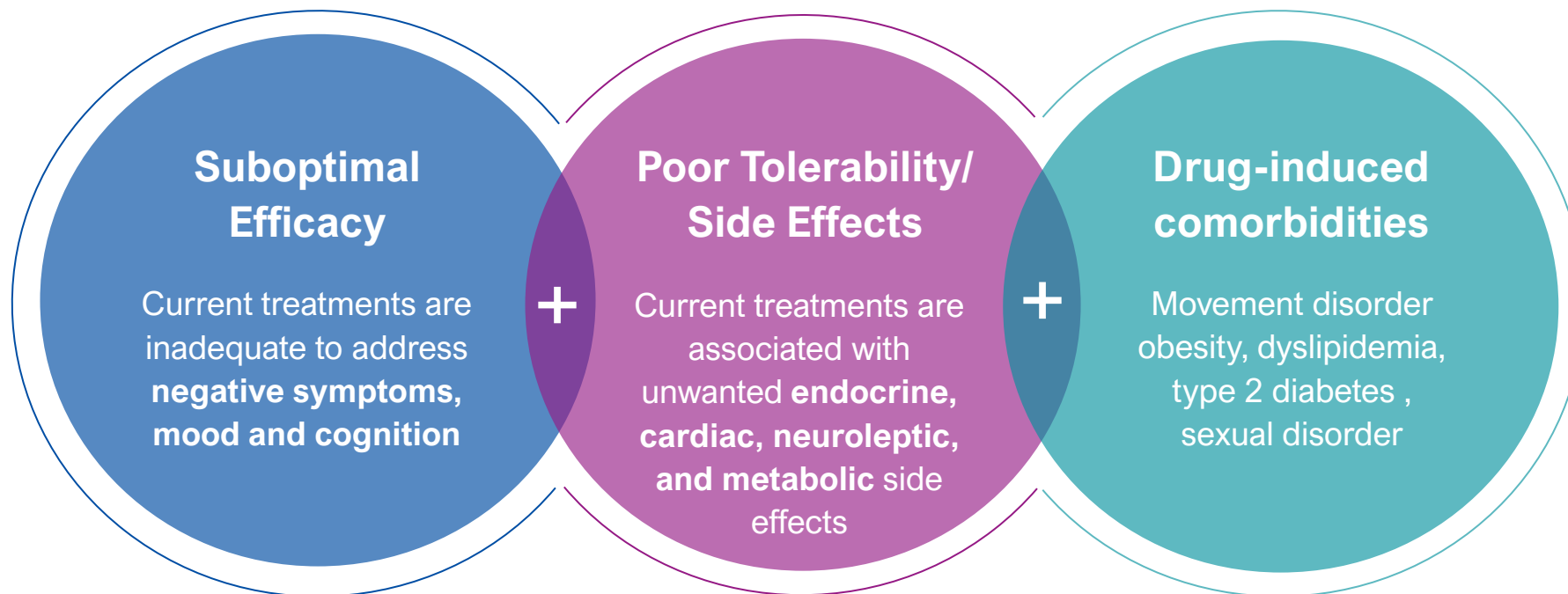
Implicated in negative symptoms and cognition

GABA receptors

Implicated in mood

No Current Therapies Address all Needs of Patients with Schizophrenia

Suboptimal efficacy and side effects limit long-term use due to high rates of discontinuation and non-compliance



Brilaroxazine Differentiation

Statistically significant results on positive symptoms, negative symptoms and cognition factor

No significant change in body weight & blood glucose levels; improvement in lipid levels, or endocrine hormones

Lower drug-drug interactions vs. standards of care

Current Treatment Paradigm has Significant Unmet Need

Schizophrenia Overview

- Impacts **~6.2M** in people in 7MM (USA, EU-4, UK & Japan) with highest in USA
- **Frequent patient switching** across antipsychotic medications
- ~50% of patients experience 1L **treatment failure**
- ~30% of patients are **treatment refractory**
- ~18% of patients **never achieve an adequate response** from any currently marketed therapies

Brilaroxazine in the Treatment Landscape

- Initial uptake **likely post-2L**, with potential to move into earlier lines of therapy
 - Potential use in 1L, pending treatment-naïve data, given efficacy & safety
- **30% estimated market share** as a 3L treatment
- Physician **enthusiasm over side effect profile**, particularly lack of weight gain and metabolic dysfunction
- Notable **ease of once daily oral administration**, with long-acting injectable representing a compelling alternative

A doctor in a white lab coat with a stethoscope around their neck is holding a large X-ray of a human torso. The X-ray shows the ribcage and internal organs. The doctor's hands are visible at the bottom of the frame. A blue diagonal line runs from the top left towards the center of the image.

Clinical Trial Results

Ongoing Clinical Program Sets the Stage for a Regulatory Path Forward

Regulatory discussions with FDA on planned New Drug Application (NDA) submission

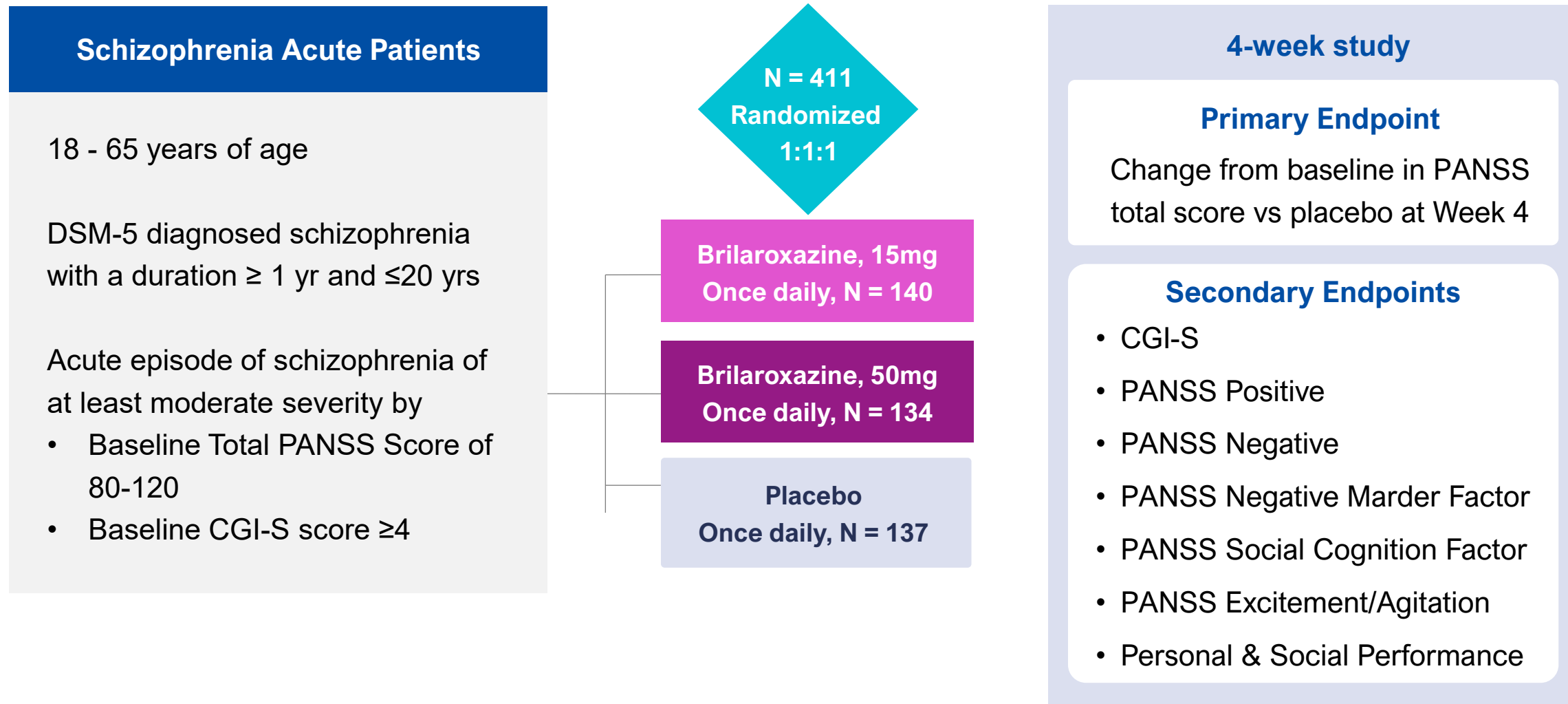
PHASE 2 REFRESH NCT01490086	✓	PHASE 3 RECOVER-1 NCT05184335	✓	PHASE 3 Long-term Safety NCT05184335	PHASE 3 RECOVER-2 TBD
N = 234 Acute schizophrenia or schizoaffective disorder		N = 411 Acute schizophrenia		N = 100 completers Stable schizophrenia	N = 450 Acute schizophrenia
Efficacy and safety		Efficacy and safety		Long-term safety and tolerability	Efficacy and safety <i>Primary and secondary endpoints consistent with RECOVER-1 trial</i>
15, 30, 50 mg		15, 50 mg		15, 30, 50 mg flexible dose	30, 50 mg
FDA indicated potential for 'Superior Safety' label claim		Completed with topline results announced in October 2023		Topline data expected Q4 2024	Completion expected Q2 2025

Registrational Phase 3 RECOVER-2 trial will replicate the successful trial design of Phase 3 RECOVER-1 trial, adjusting for study time length and dosing

Most non-clinical development is complete, and preparation is underway to file in Q3 2025

Completed Phase 3 RECOVER-1 Trial for Schizophrenia

Randomized, 4-week, double-blind, placebo-controlled, multicenter trial in acute exacerbation of schizophrenia



Brilaroxazine Key Points of Clinical Differentiation

Favorable efficacy and safety profile in brilaroxazine vs placebo at week 4

Efficacy in Brilaroxazine 50 mg vs Placebo

Significant Treatment effects on major symptom domains of schizophrenia:

- ✓ **10.1-point reduction in PANSS total score**
- ✓ **78% patients had ≥ 1 -point decrease in CGI score**
- ✓ 2.8-point reduction in positive symptoms
- ✓ 2-point reduction in negative symptoms
- ✓ 1.6-point reduction in social cognition deficits
- ✓ 2.1-point reduction in agitation/excitement
- ✓ Improvement in personal & social function
- ✓ Improvement in sexual functioning (females)
- ✓ Decrease in key proinflammatory cytokines

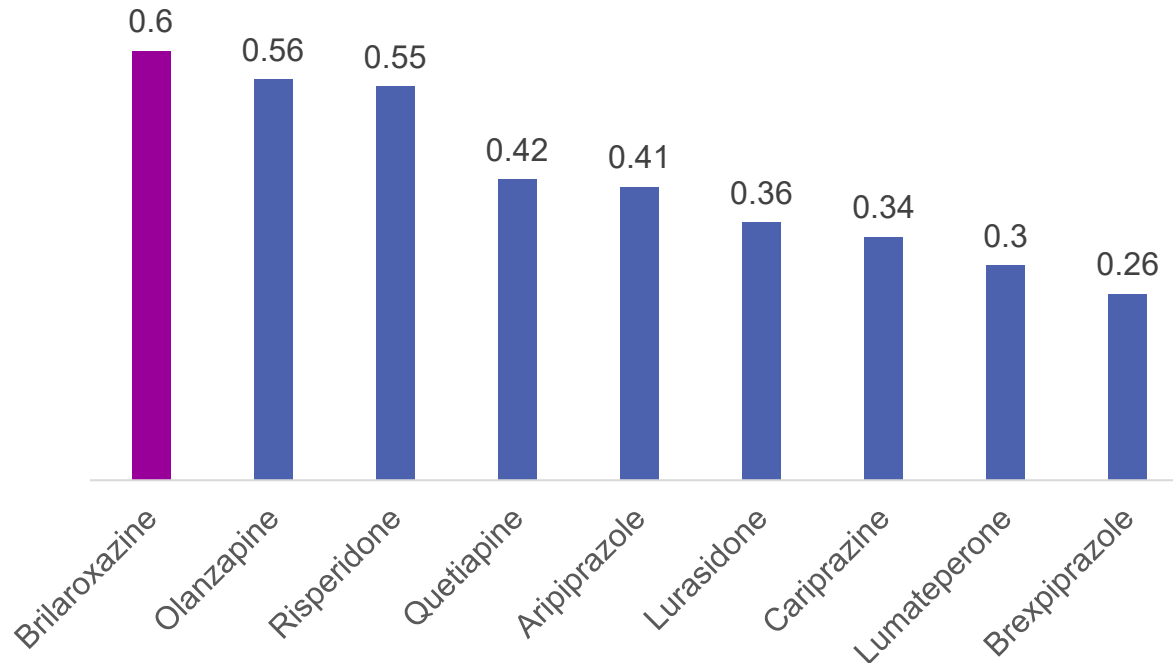
Safety & Tolerability

- **Compliance:** Discontinuation rate 16% in 50 mg, 19% in 15 mg, 22% in placebo
- **Metabolic:** Decrease in lipids vs placebo. Weight gain 3 (2.1%) in 15 mg, 8 (5.9%) in 50 mg, 4 (2.9%) in 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:** No cardiac and GI side effects
- No incidence of suicidal ideation or suicides

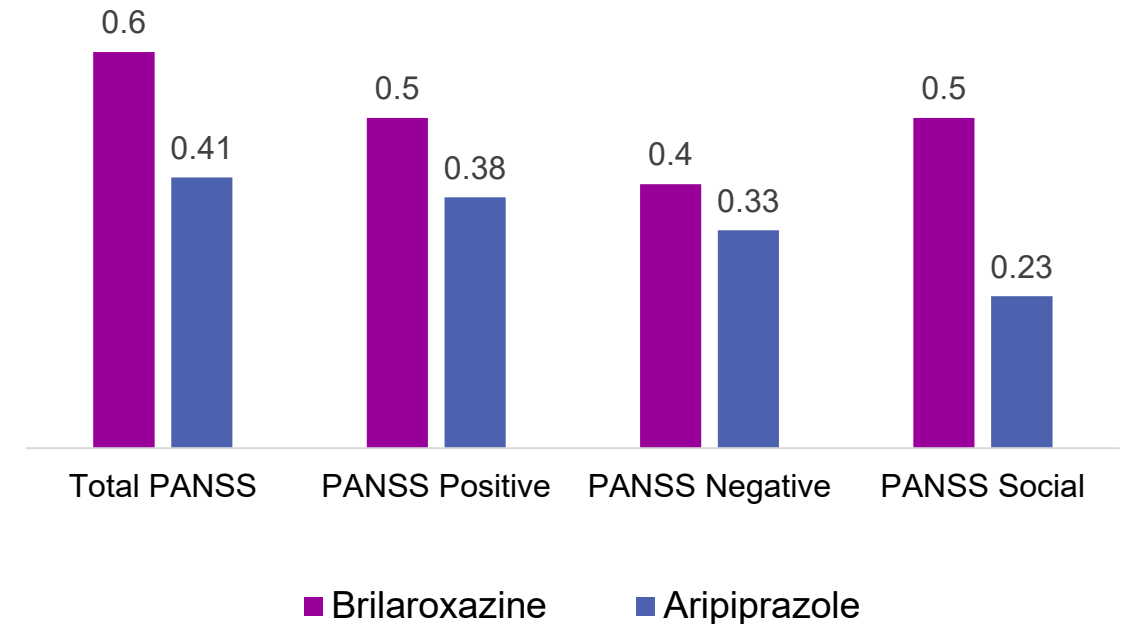
Comparison of Treatment Effect Size from Phase 3 Studies

Primary endpoints and major secondary efficacy endpoints

Brilaroxazine¹ vs Marketed Antipsychotics^{2,3}



Brilaroxazine¹ vs Aripiprazole²



RECOVER-1 Trial Demographics and Baseline Characteristics

Balanced randomization with diverse representation of 411 patients; USA 60%, India 34%, Bulgaria 6%

	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)

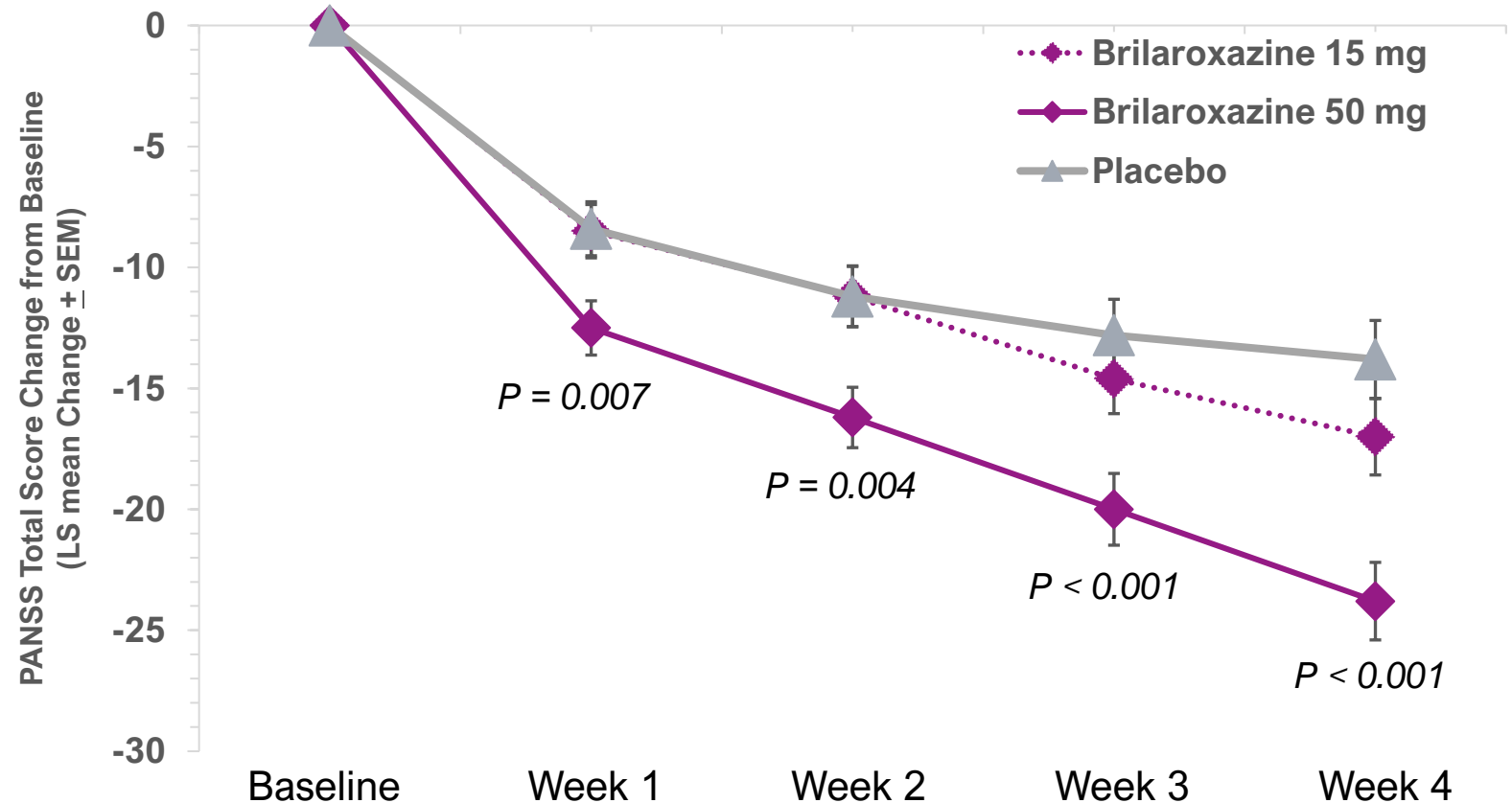
RECOVER-1 Trial Primary Endpoint: PANSS Total Score

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)

Cohen's d effect size of 0.6

PANSS Total Score

- Successfully met PANSS Total Score primary endpoint for brilaroxazine 50 mg
- Statistically significant and clinically meaningful sustained decrease with brilaroxazine 50 mg
- Separation for brilaroxazine 50 mg from placebo within a week
- Brilaroxazine 15 mg numerically separated from placebo

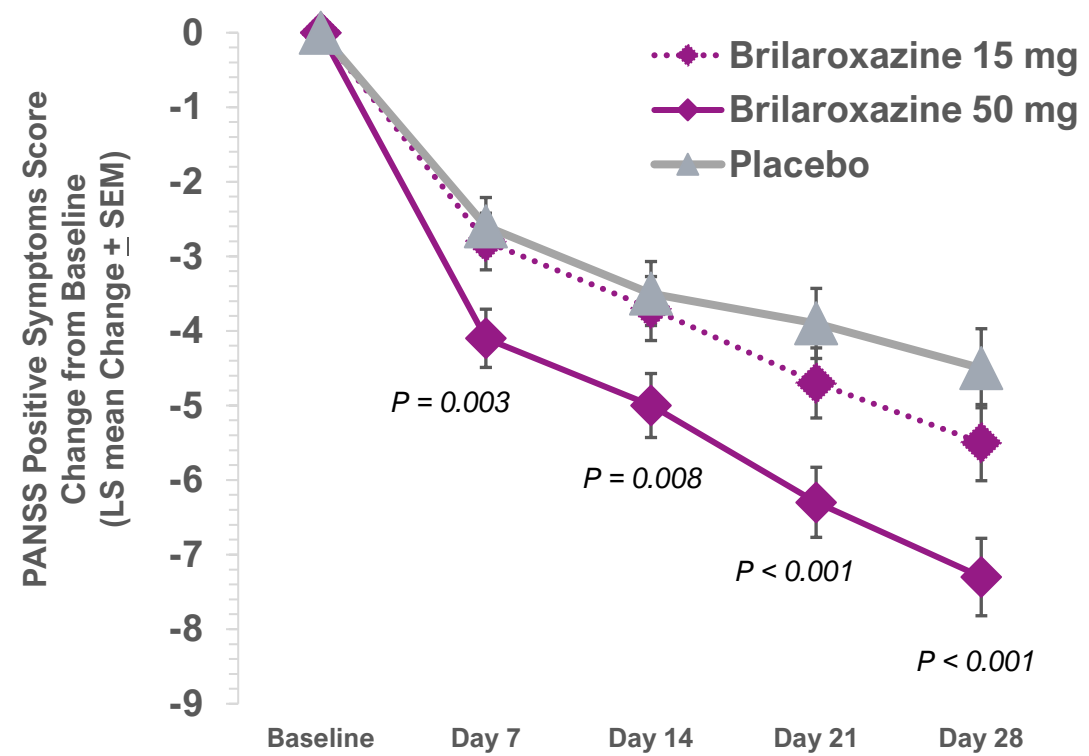


RECOVER-1 Secondary Endpoints: Positive Symptoms and Agitation/Excitement

Significant decrease in positive symptoms and agitation/excitement in brilaroxazine 50 mg vs. placebo at week 4

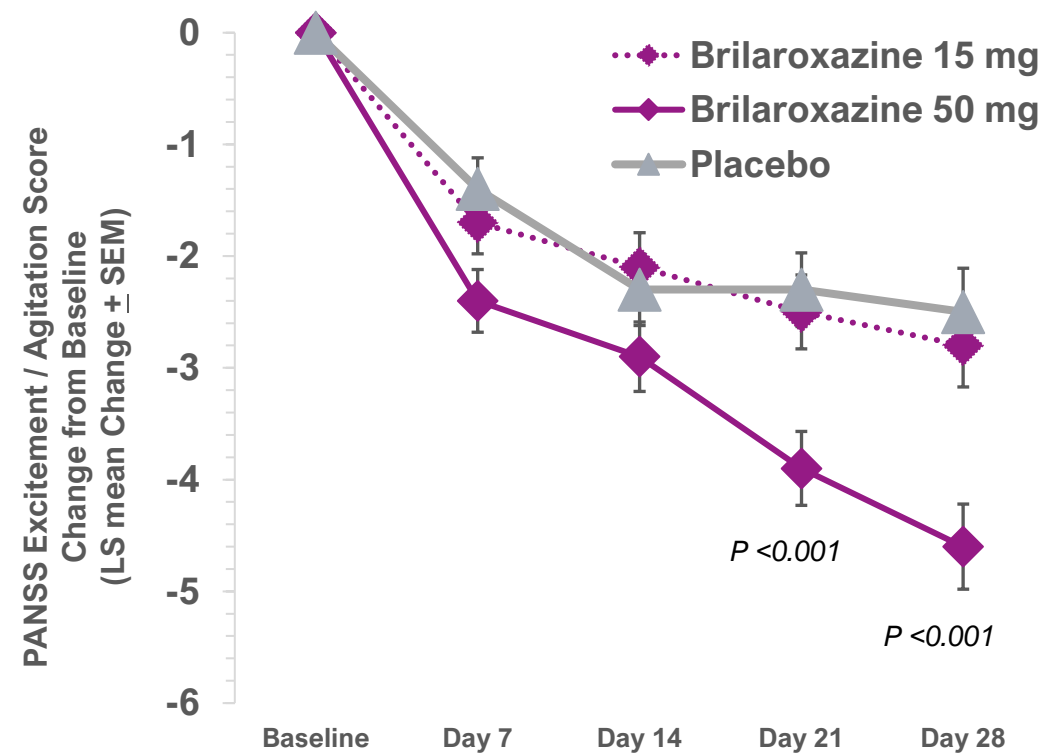
Decrease in Positive Symptoms

Cohen's d effect size of 0.5



Decrease in Agitation/Excitement Symptoms

Cohen's d effect size of 0.5

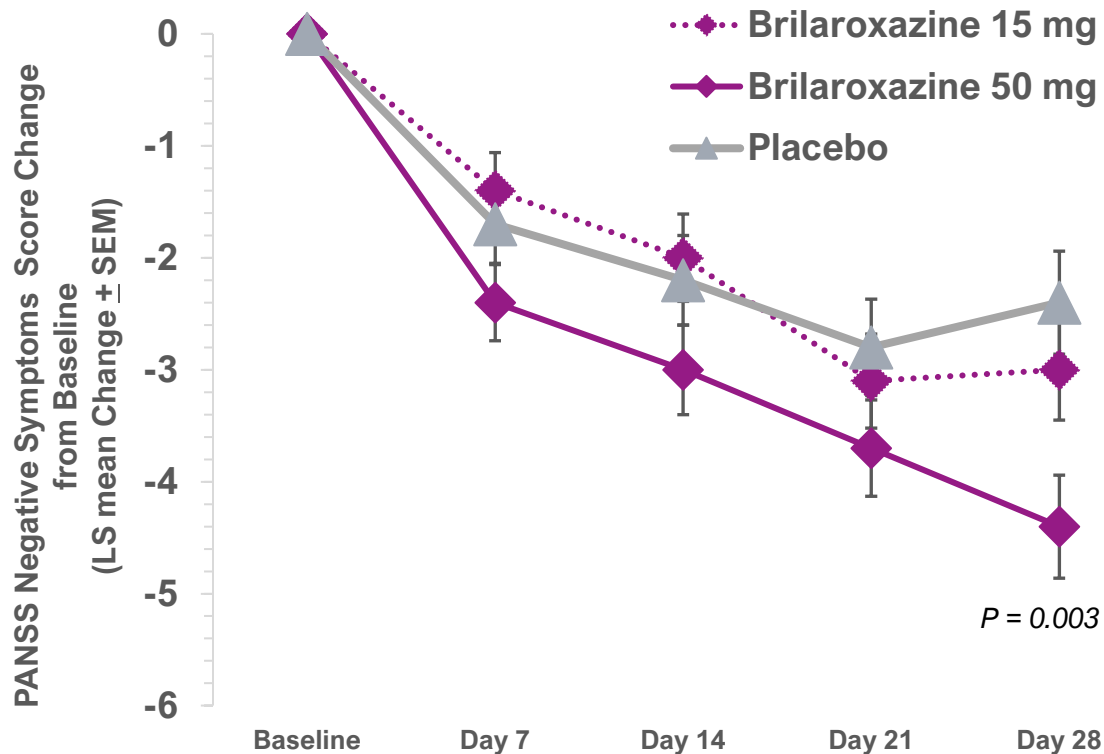


RECOVER-1 Secondary Endpoints: Negative Symptoms

Significant decrease in negative symptoms in brilaroxazine 50 mg vs. placebo at week 4

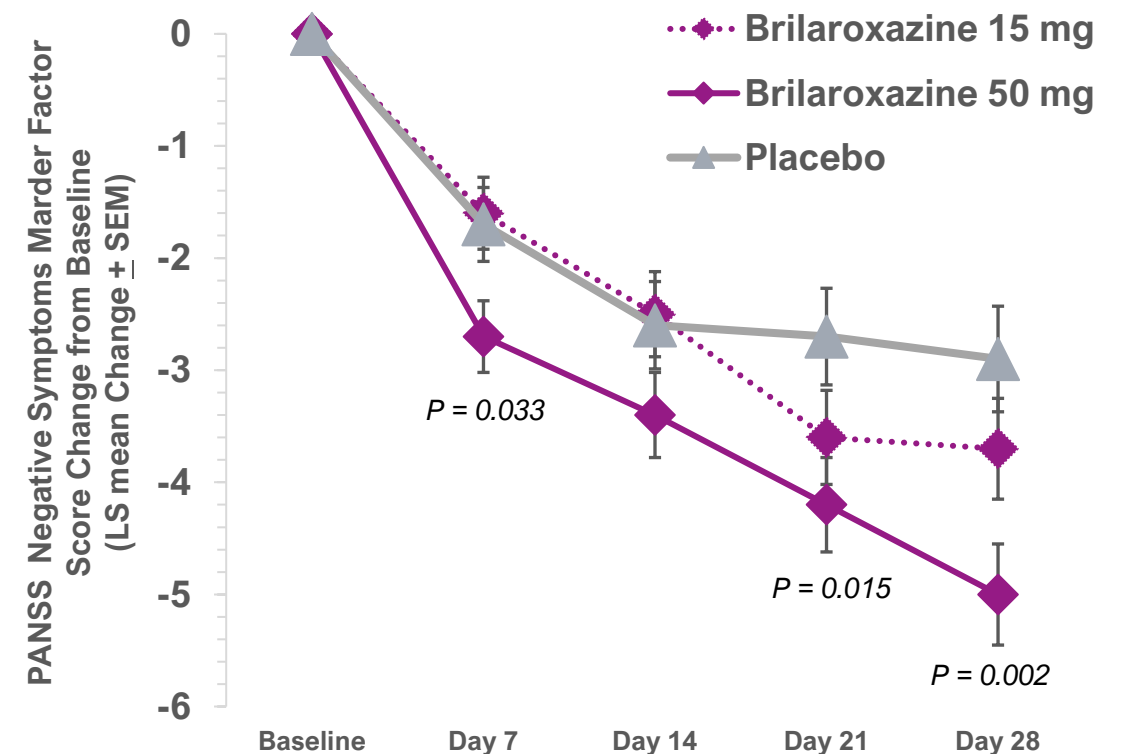
Decrease in Negative Symptoms

Cohen's d effect size of 0.4



Decrease in Negative Symptoms (Marder Factor)

Cohen's d effect size of 0.4

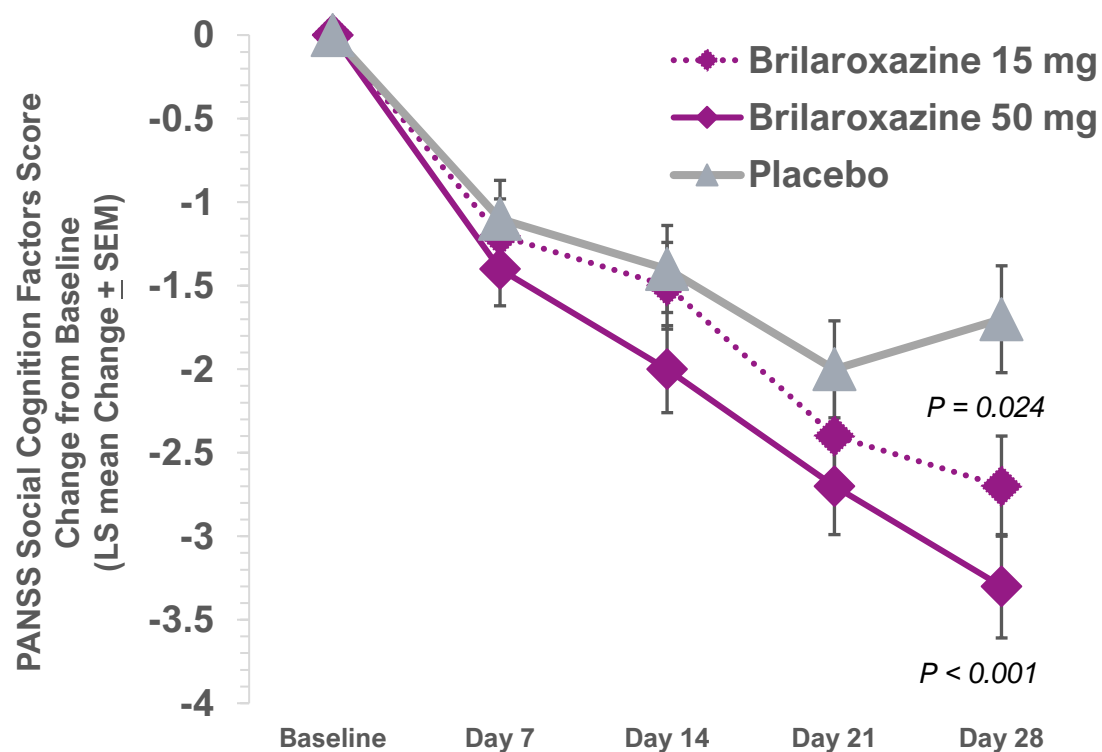


RECOVER-1 Secondary Endpoints: Social Cognition and Social Functioning

Significant decrease in social cognition deficits and improvement in personal & social performance

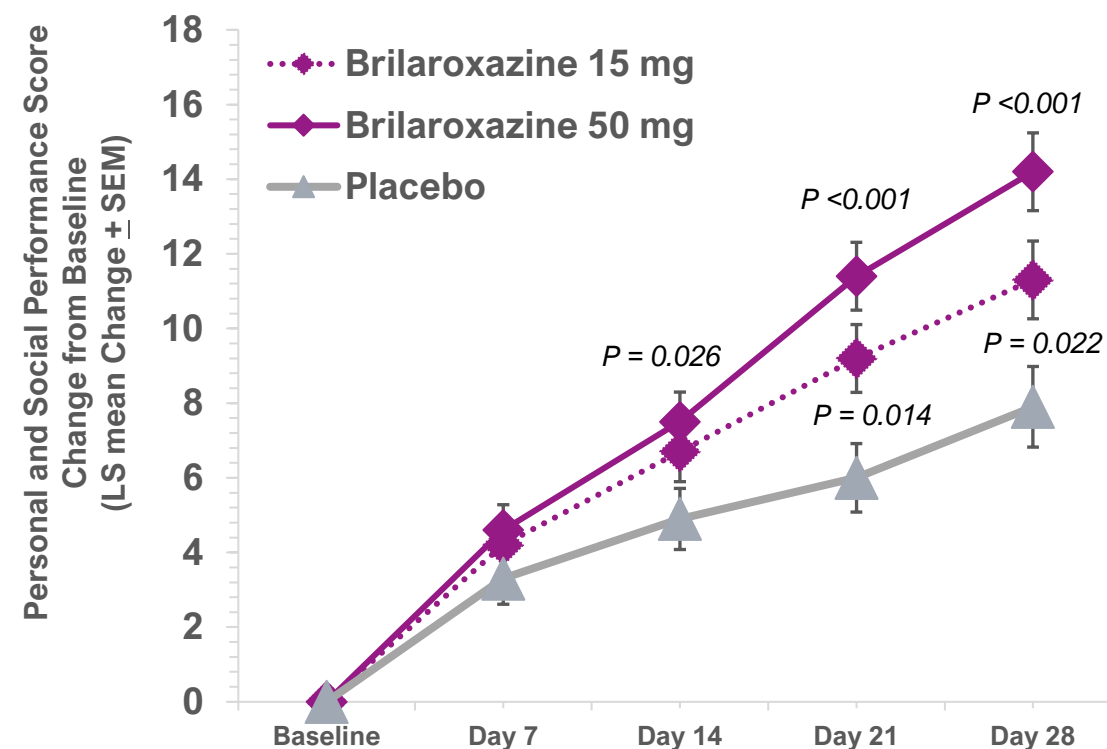
Decrease in Social Cognition Deficits

Cohen's d effect size of 0.5



Improvement in Personal and Social Performance

Cohen's d effect size of 0.5

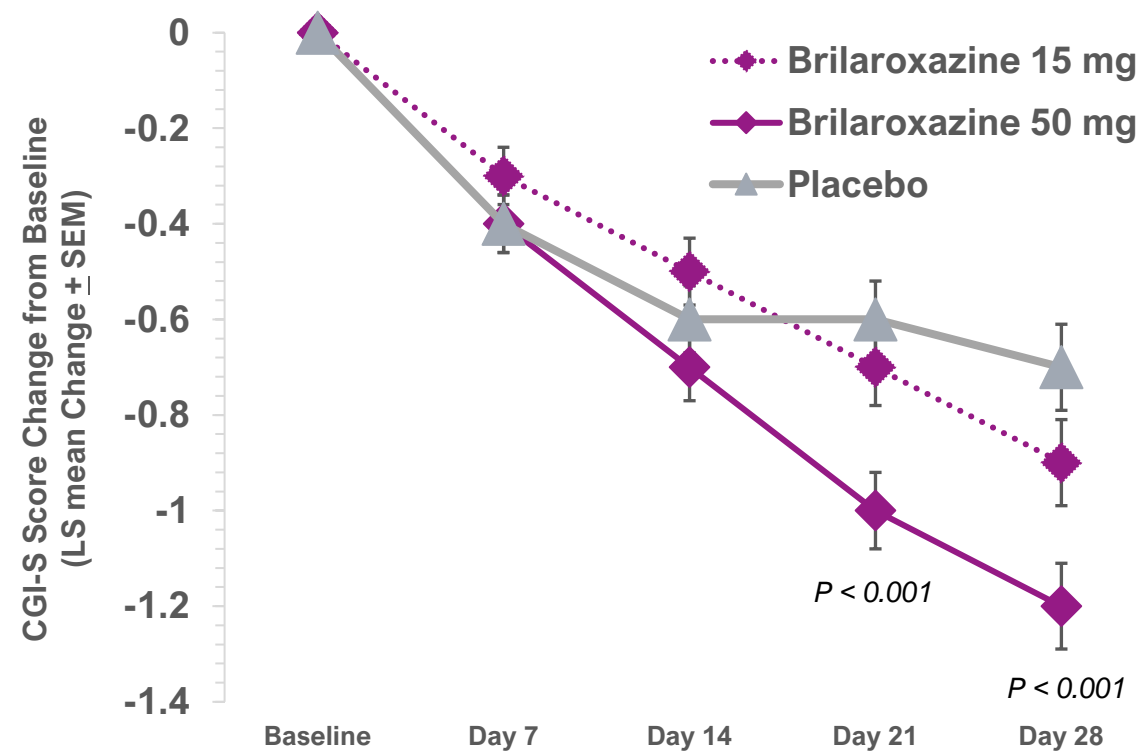


RECOVER-1 Trial Secondary Endpoint: CGI-S Scores

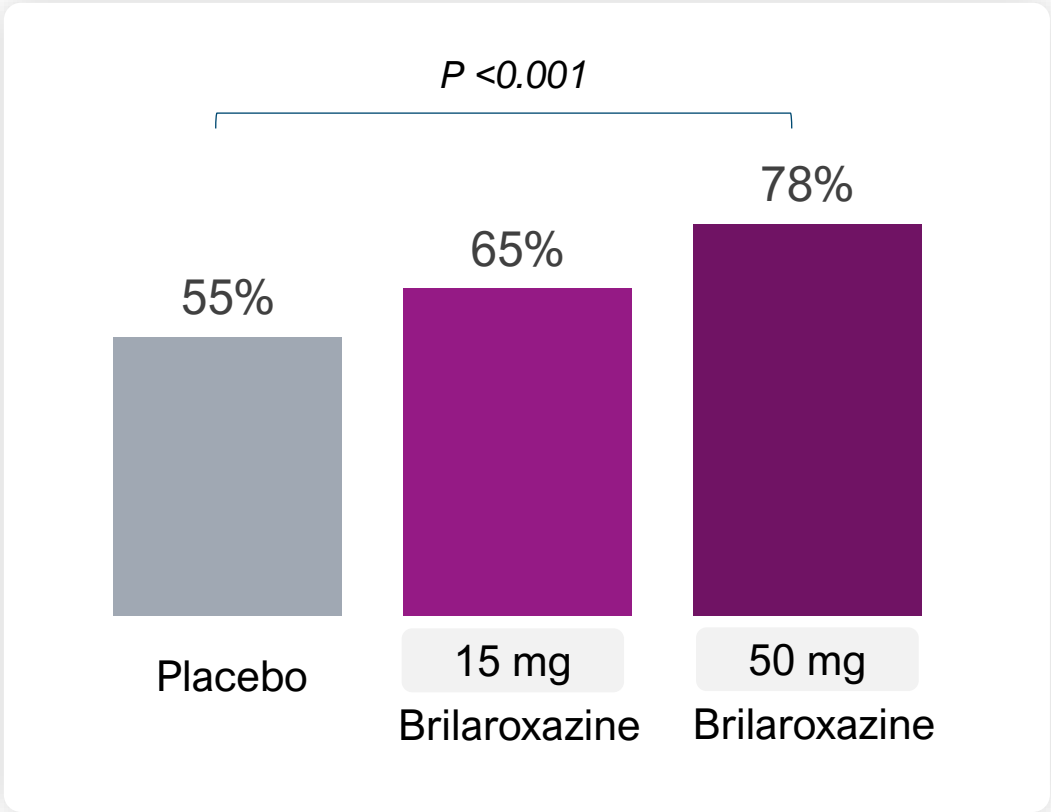
≥1-Point reduction in CGI-S score in brilaroxazine 50 mg vs. placebo at week 4, $p < 0.001$

CGI-S Score ≥ 1-Point Reduction

Cohen's d effect size of 0.5



Proportion of Subjects with ≥ 1-Point Reduction



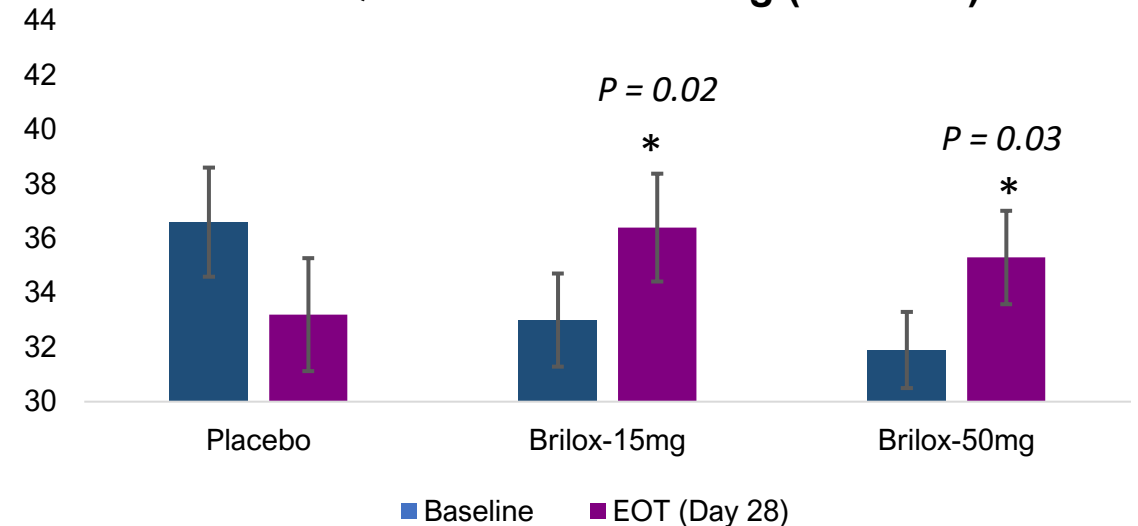
RECOVER-1 Trial: Sexual Functioning CSFQ Score

Significant improvement in sexual functioning with Brilaroxazine vs Placebo (Females)

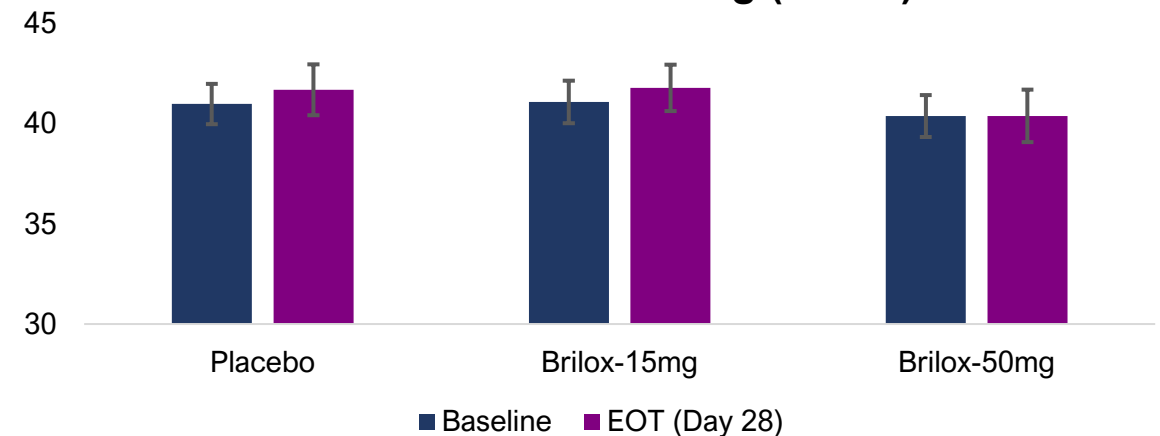
Sexual Functioning

- Brilaroxazine (15 and 50 mg) significantly improved sexual functioning in females and comparable to placebo.
-
- CSFQ scores ≤ 41 for females and ≤ 47 for males indicate sexual dysfunction
 - Prevalence of sexual dysfunction in women 60% and men 55% men with schizophrenia
 - Sexual dysfunction linked to negative symptoms, social cognition and social functioning
 - Sexual dysfunction impacts quality of life, treatment adherence, and may develop depression and suicidality
 - Hyperprolactinemia and hypothyroidism in schizophrenia linked sexual dysfunction

CSFQ: Sexual Functioning (Females)



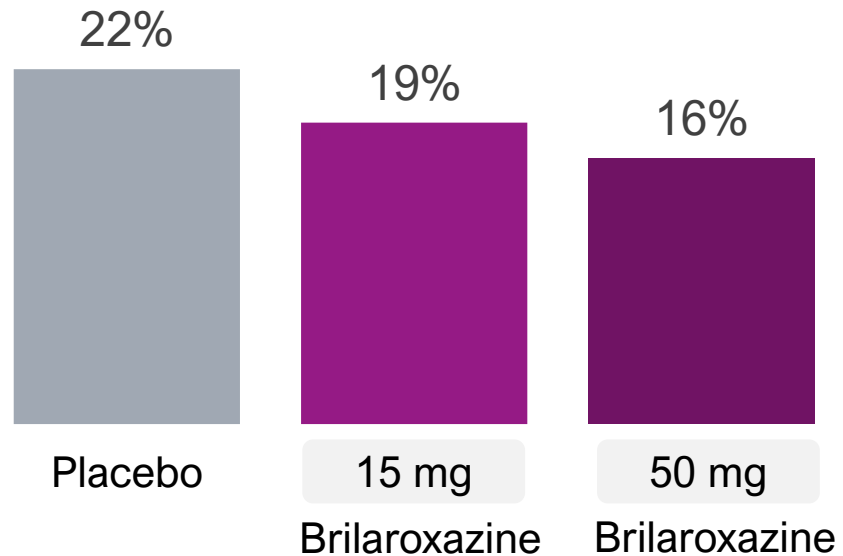
CSFQ: Sexual Functioning (Males)



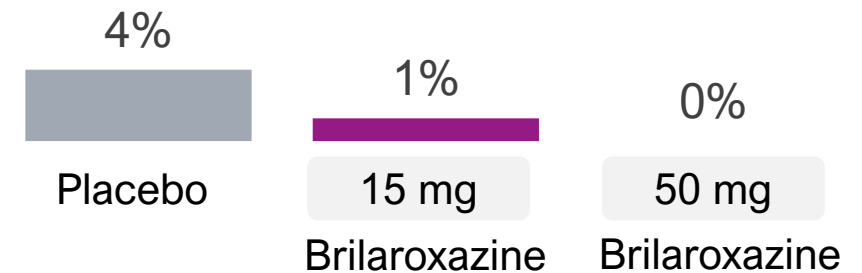
RECOVER-1 Trial Discontinuation Rates: Brilaroxazine vs. Placebo

Low discontinuation rates in brilaroxazine treatment groups vs placebo

Discontinuation Rate



Discontinuation Due to Side Effects



RECOVER-1 Trial Topline Tolerability Results: Brilaroxazine vs Placebo

Well-tolerated safety profile

Brilaroxazine was generally well tolerated

- Overall TEAEs rates 34.5% in brilaroxazine 15 mg, 35.5% in 50 mg, and 30% in placebo
- No serious adverse events (SAEs) related to the study drug brilaroxazine
- No incidence of suicidal ideation
- No significant change in bodyweight and blood glucose levels vs placebo
- Decrease in cholesterol, LDL and triglycerides and increase in HDL vs placebo
- Common brilaroxazine TEAEs were headache (<6%) and somnolence ($\leq 7.5\%$) generally transient in nature

Brilaroxazine adverse events of special interest (AESI) were mild to moderate in severity

- Metabolic Side Effects:
 - Weight gain 3 (2.1%) in 15 mg and 8 (5.9%) in 50 mg brilaroxazine and 4 (2.9%) in placebo
 - Elevated LDL level none in brilaroxazine and 4 (2.9%) in placebo
 - Low HDL level 1 (0.7%) in 15 mg, 2 (1.4%) in 50 mg brilaroxazine and 2 (1.4%) in placebo
- Neuroleptic Side Effects:
 - Akathisia 1 (0.7%) and EPS 1 (0.7%) in 50 mg brilaroxazine and none in 15 mg and placebo
- Endocrine Side effects:
 - Significant decrease in prolactin and no change in thyroid levels compared placebo

RECOVER-1 Trial: Change in Bodyweight

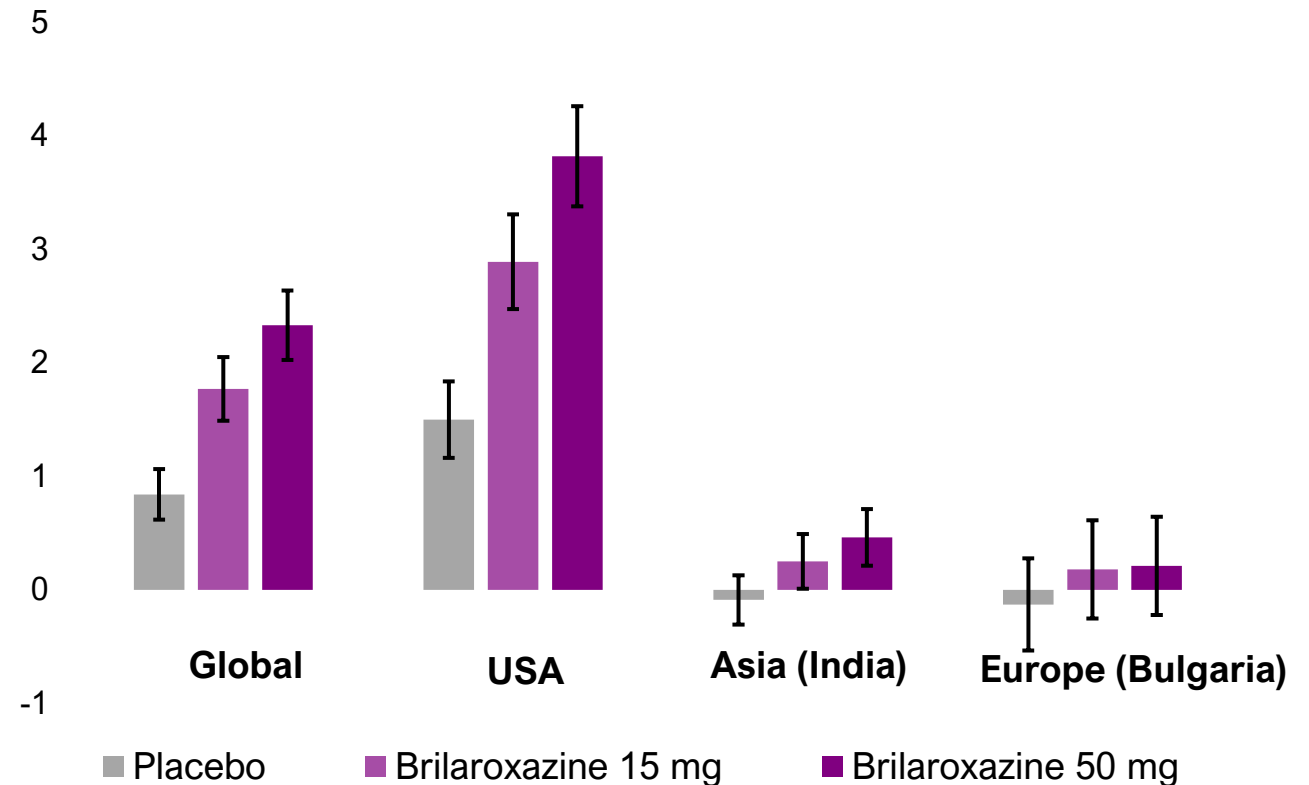
Global and regional analysis of change in bodyweight in brilaroxazine vs placebo

Change in Bodyweight (kg)

- No clinically significant weight gain in brilaroxazine vs placebo
- Subjects in USA had ~30% higher baseline bodyweight compared to ex-USA subjects
- Subjects from USA reported higher weight gain compared to subjects from ex-USA (Bulgaria/India)
- Weight gain AESI reported in 15 subjects: N=3 (2.1%) in 15 mg and N=8 (5.9%) in 50 mg brilaroxazine and N=4 (2.9%) in placebo
- Among AESI weight gain (N=15) reported in this study, 13 are in the USA and 2 are from ex-USA

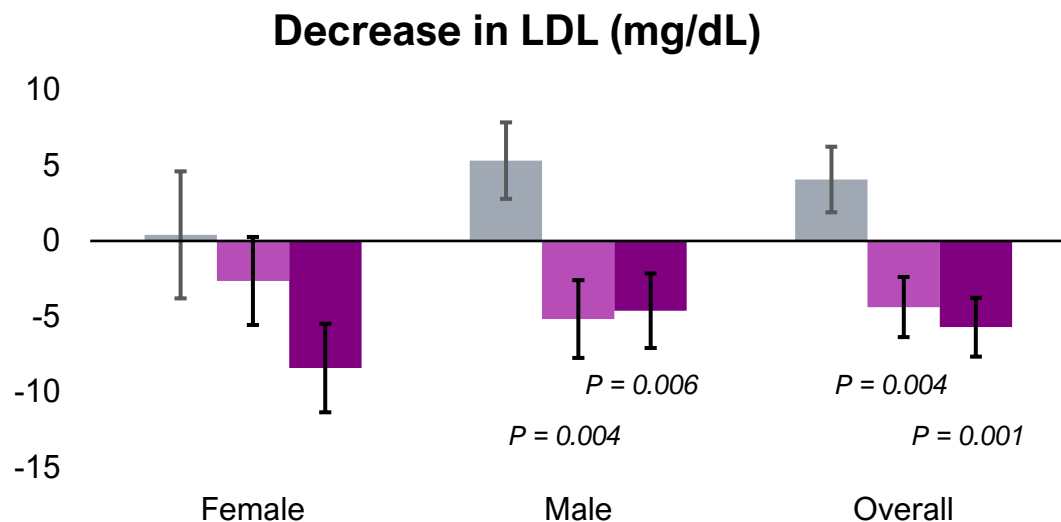
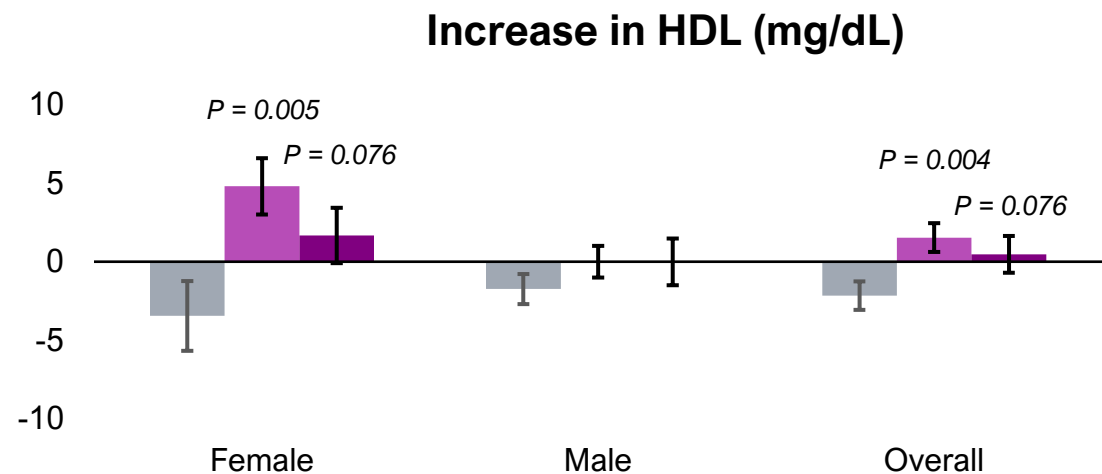
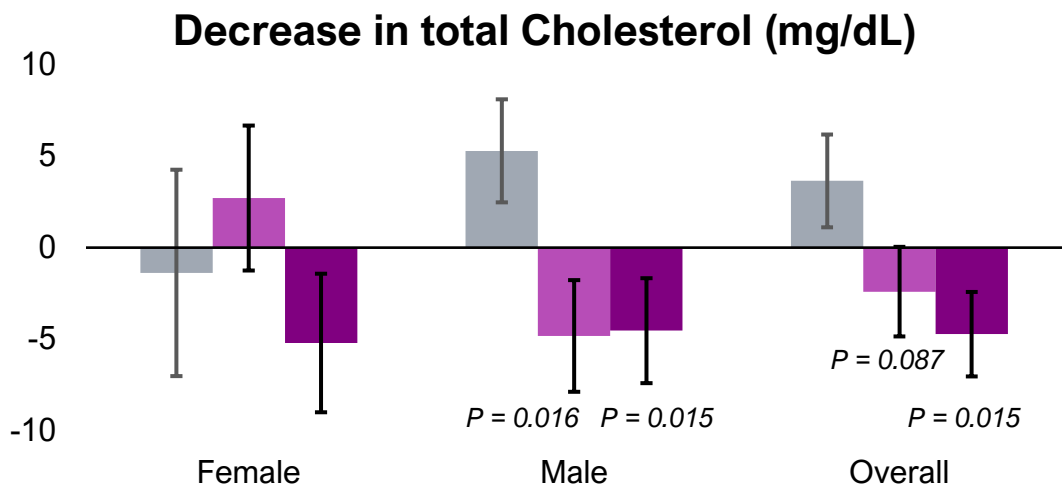
Mean Change in Bodyweight (kg)

Global (N=411): USA (N=245), India (N=140), Bulgaria (N=26)



RECOVER-1 Trial: Change in Lipids

Clinically significant decrease in Cholesterol, LDL, and Increase in HDL in Brilaroxazine vs Placebo



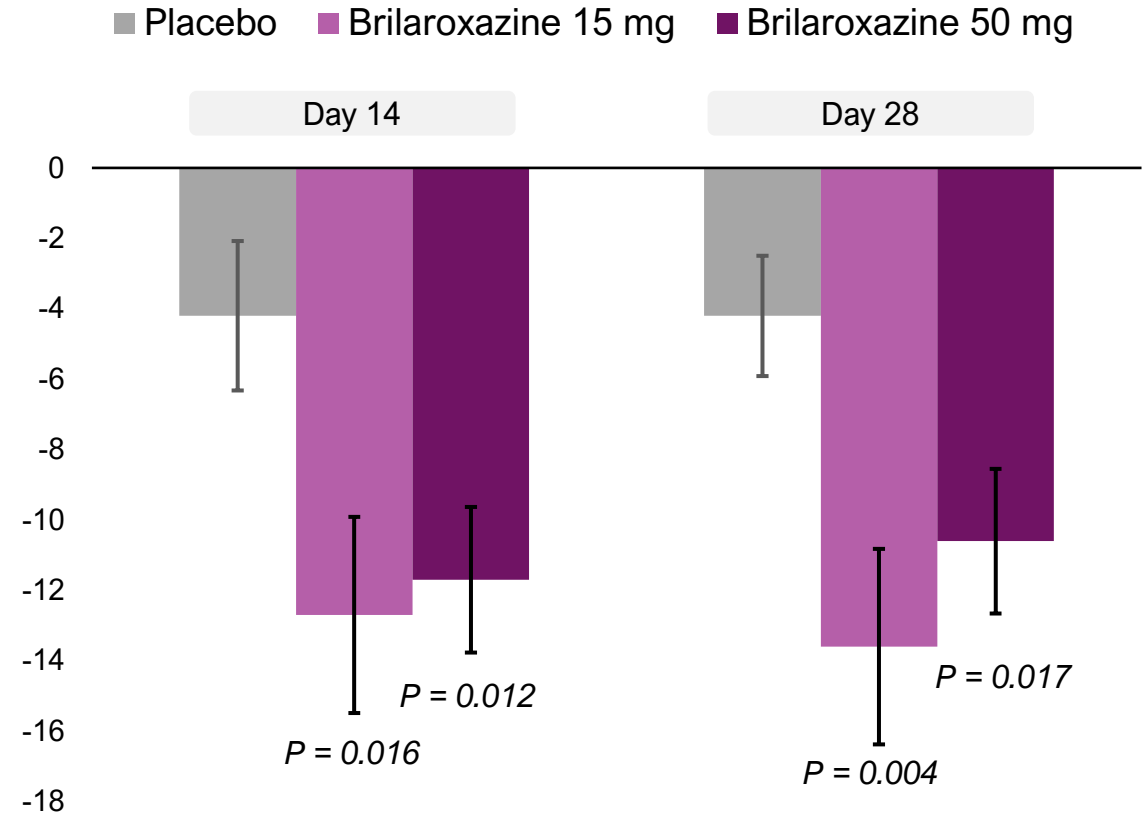
RECOVER-1 Trial: Change in Prolactin Hormone

Clinically significant decrease in prolactin hormone levels in brilaroxazine (15 and 50mg) vs placebo

Decrease in Prolactin

- Clinically significant decrease in prolactin levels on Day 14 and Day 28 in brilaroxazine (15 and 50 mg) vs placebo
- Hyperprolactinemia is common condition in patients with schizophrenia / psychiatric disorders
- Hyperprolactinemia is associate with immune disorders / diseases and believed to play crucial role in their pathogenesis
- Hyperprolactinemia is associated with variety of adverse effects: weight gain, breast tenderness and enlargement, sexual dysfunction (lack of libido), and erectile dysfunction in men.

Decrease in Serum Prolactin (mIU/L)



RECOVER-1 Trial: Change in Brain-Derived Neurotrophic Factor (BDNF)

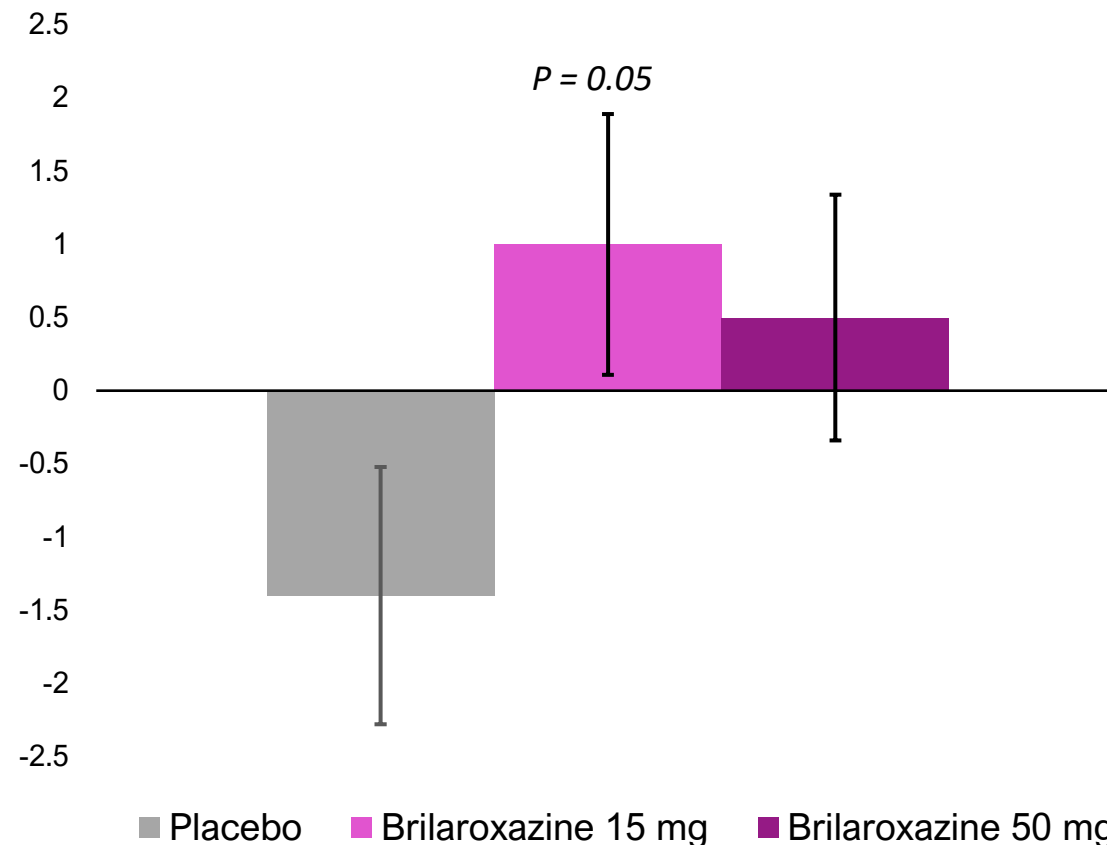
Clinically significant improvement in BDNF levels with Brilaroxazine 15 mg vs Placebo

BDNF Improvement

- Brilaroxazine improved BDNF compared to placebo, 15mg dose showed significant improvement.

- Reduced levels of BDNF reported in schizophrenia and depression patients
- BDNF is linked to negative symptoms and cognitive / memory impairments in schizophrenia
- BDNF is linked with neuroinflammation
- Improvement in BDNF levels reported to decrease proinflammatory cytokine levels (e.g. IL-6, IL-8 etc) in schizophrenia and depression patients

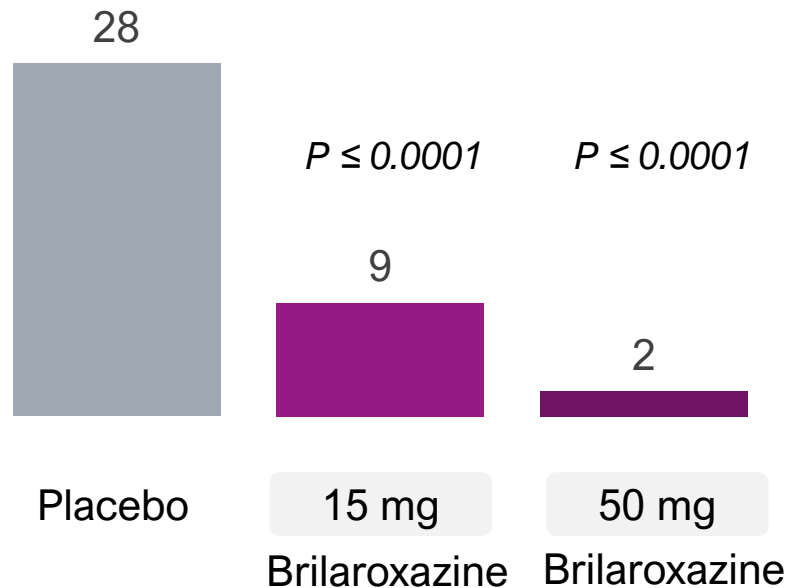
Improvement in Serum BDNF (ng/mL)



RECOVER-1 Trial: Change in Proinflammatory Serum Cytokines & Chemokines

Clinically significant decrease in cytokine IL-8 and chemokine MIP-1 in Brilaroxazine vs Placebo

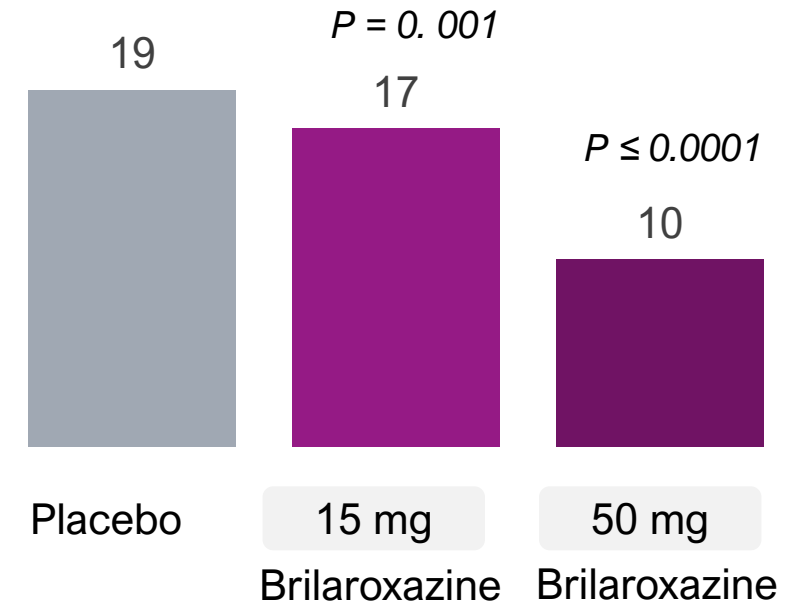
Decrease in Proinflammatory Cytokine IL-8 (ng/mL)



Elevated IL-8 levels have been reported in psychiatric diseases, particularly in schizophrenia, bipolar disorder, obstructive sleep apnea and autism spectrum disorder

(Tasi S-J. Prog Neuropsychopharmacol Biol Psychiatry 2021)

Change in Proinflammatory Chemokine MIP-1 (ng/mL)



Elevated level of MIP-1 found in schizophrenia, depression and Alzheimer's patients

(Frydecka D et al. Brain Behavior and immunity 2018,; Hong S et al Schizophrenia Res 2016)

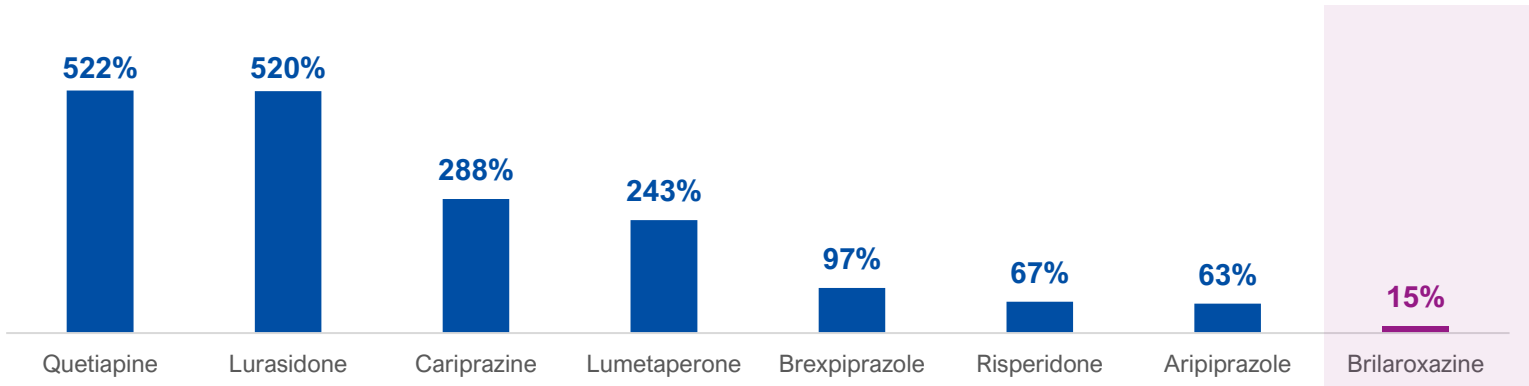
Lower Drug-Drug Interactions (DDIs) with Brilaroxazine vs. Standards of Care

DDIs and polypharmacy alter plasma drug concentrations, and can impact efficacy and side effect profiles of a drug¹¹ | ~50% of prescribed drugs and over 25% of approved antipsychotics are known to cause drug interactions in the presence of a strong CYP3A4 inhibitor drug

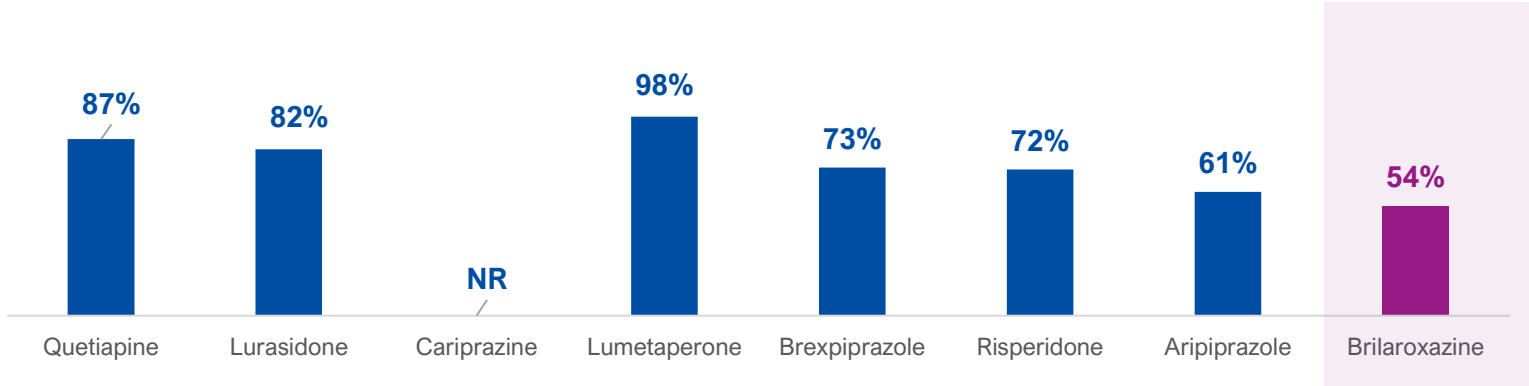
Change in drug concentration with a CYP3A4 Inhibitor	
Antipsychotic	Fold increase vs brilaroxazine
Brilaroxazine	--
Aripiprazole	4.2x
Risperidone	4.5x
Brexpiprazole	6.5x
Lumetaperone	16.2x
Cariprazine	19.2x
Lurasidone	34.7x
Quetiapine	34.8x

*Olanzapine⁹ not evaluated; metabolized by CYP1A2¹⁰

% Increase in drug concentration (AUC) with a **CYP3A4 Inhibitor**



% Decrease in drug concentration (AUC) with a **CYP3A4 Inducer**



Lower is better

Brilaroxazine: Consistent Findings in 50 mg Dose in Phase 2 and Phase 3 Studies

Robust efficacy on primary endpoint and key secondary endpoints and low discontinuation rate, lower than placebo

Key Metrics	PHASE 3 RECOVER (N=411 4-wk) NCT05184335	PHASE 2 REFRESH (N=234 4-wk) NCT01490086
Primary Endpoint (Brilaroxazine 50 mg vs Placebo)		
PANSS Total Score	-10.1 P<0.001 (Effect Size, 0.6)	-10.7 P<0.01
Secondary Endpoint (Brilaroxazine 50 mg vs Placebo)		
PANSS Positive Score	-2.8 P<0.001 (Effect Size, 0.5)	-3.04 P=0.03
PANSS Negative Score	-2.1 P<0.003 (Effect Size, 0.4)	-2.04 P=0.04
CGI-S Score	-0.5 P<0.001 (Effect Size, 0.5) Improvement ≥ 1, 78%	-0.5 P=0.02 Improvement ≥ 1, 72%
Discontinuation Rate (Brilaroxazine 50 mg vs Placebo)		
Related to any reasons	16% (50mg) vs 22% (placebo)	12% (50mg) vs 28% (placebo)
Related to TEAEs in 50mg	0	1.7% (1-subject)

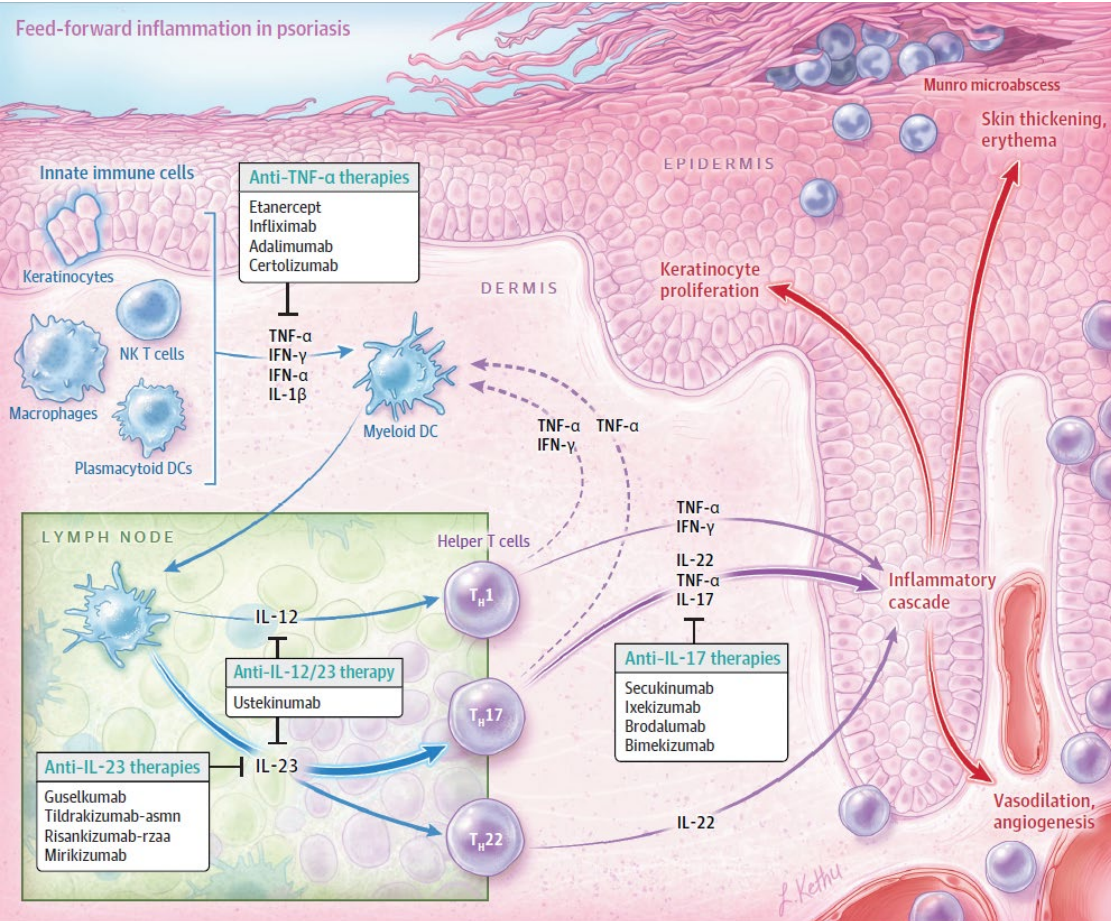
A doctor in a white lab coat with a stethoscope around their neck, holding a large X-ray of a human chest. The X-ray shows the ribcage and lung fields. The doctor is standing in front of a window with a blue frame.

Inflammatory / Immune Disease Programs

Psoriasis | Pulmonary Arterial Hypertension (PAH) |
Idiopathic Pulmonary Fibrosis (IPF)

Brilaroxazine has Potential to Treat Psoriasis

Inflammatory skin disease driven by dysfunctional serotonin-dopamine signaling

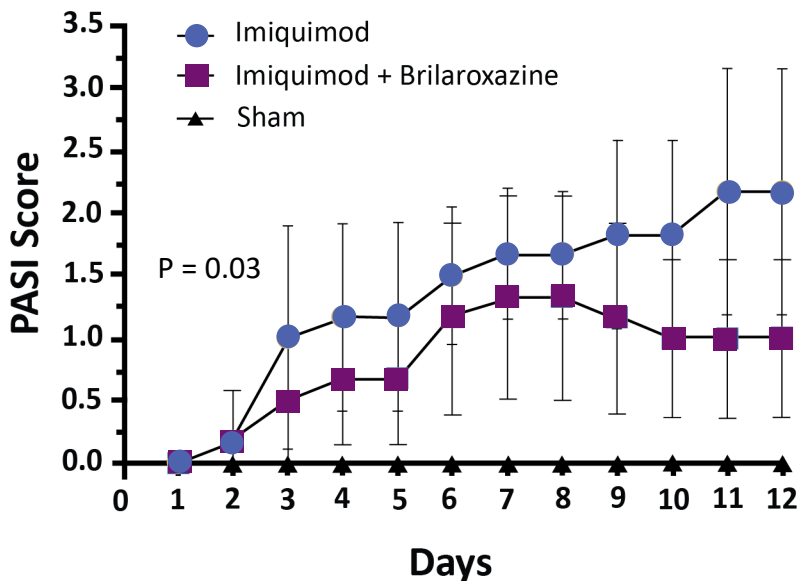


- Approx 3% of the US population and an estimated 125 million people worldwide suffer from psoriasis
- An estimated one-third of neuropsychiatric and neurodegenerative disease patients suffer from psoriasis
- Currently there is no cure for psoriasis
 - Topical corticosteroids therapies remain the cornerstone for treating mild psoriasis
 - Biologics that inhibit cytokines TNF-α, p40IL-12/13, IL-17, and p19IL-23, and oral PDE-4 inhibitor for moderate to severe plaque psoriasis

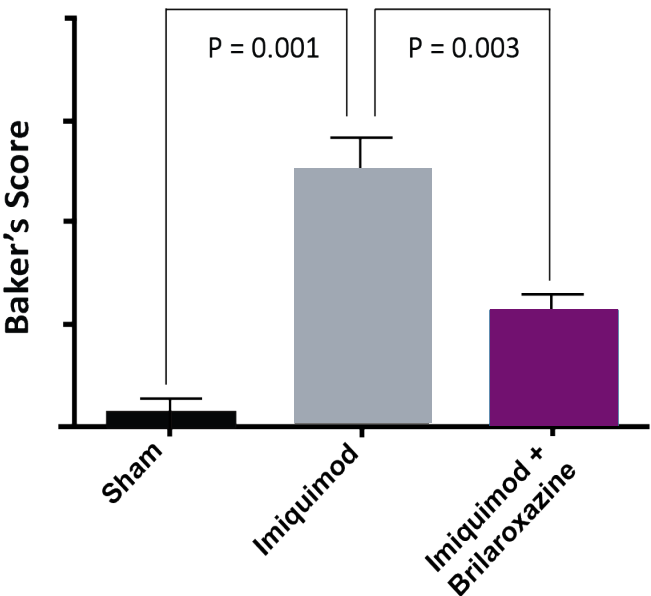
Brilaroxazine Demonstrated Encouraging Preclinical Efficacy

In an imiquimod induced mouse model of psoriasis

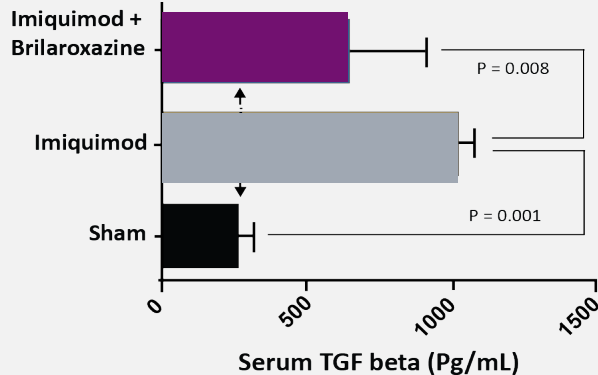
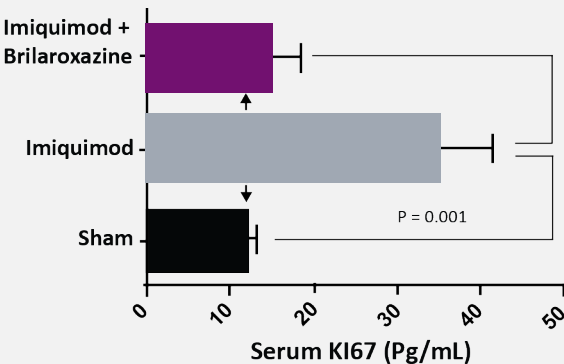
Psoriasis Area Severity Index (PASI)



Psoriasis Severity by Baker Score



Decrease in anti-inflammatory and proliferation cytokine (KI67) and profibrotic chemokine (TGF-β)



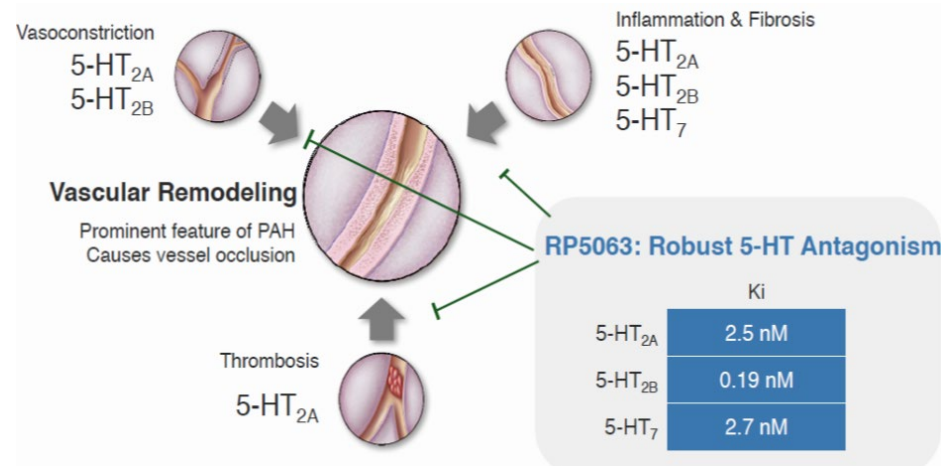
Brilaroxazine topical liposomal gel significantly decreased

- Psoriasis area severity index (P= 0.03)
- Clinical severity of psoriasis, Baker score (p=0.003)
- Proinflammatory and proliferation cytokine, KI67 (P=0.001)
- Profibrotic chemokine, TGF-β (P=0.001)

Brilaroxazine: Potential to Delay PAH and IPF Disease Progression

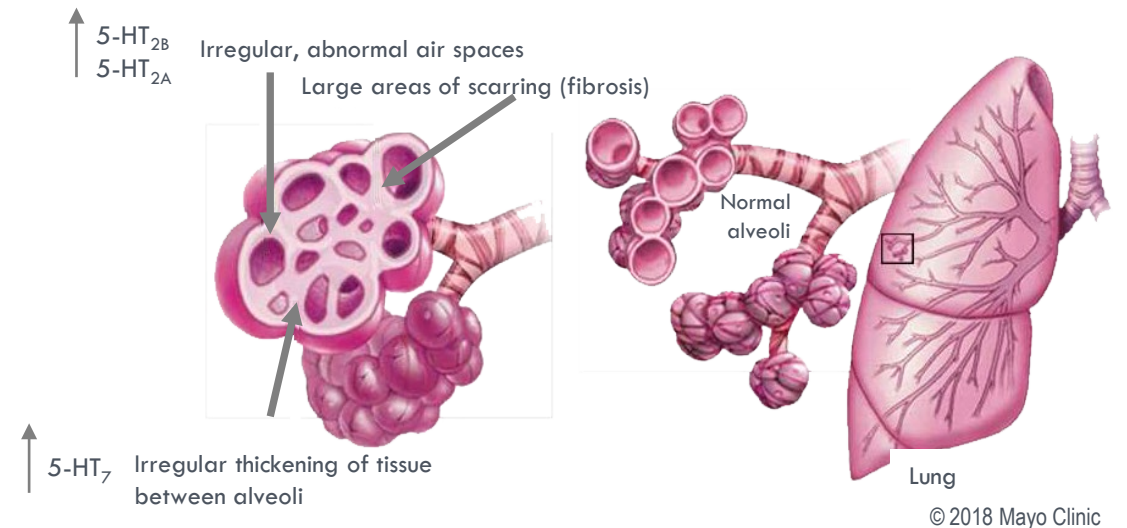
PAH and IPF are Orphan Diseases that involve dysfunctional serotonin signaling

Lung Vascular Remodeling in PAH



- PAH and IPF are rare, chronic, and debilitating conditions
- No therapies significantly delay disease progression
- Patients experience elevated plasma serotonin (5-HT) levels, increased expression of 5-HT_{2A/2B/7} receptors & inflammatory cytokines in lungs

Lung Alveoli Remodeling in IPF



- Lung vascular/alveoli remodeling occurs due to inflammation, fibrosis, and pulmonary hypertension
- Brilaroxazine has robust antagonism against serotonin receptors involved in vasoconstriction, fibrosis, blood clots, and inflammation

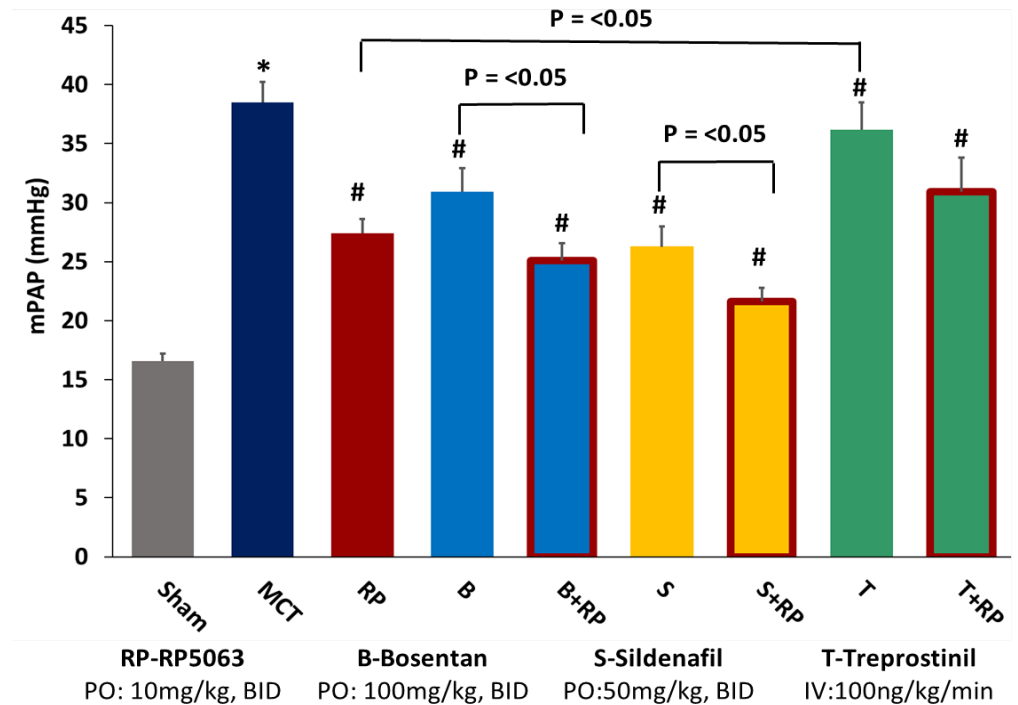
Brilaroxazine: Encouraging Results in PAH Translational Rodent Models

Potential for Improved Treatment Effect Compared to Standard of Care

Brilaroxazine alone and co-administered with standard of care for PAH

- Mitigated PAH in MCT and Sugen-Hypoxia rodent models
- Decreased respiratory resistance and restored blood oxygen saturation
- Decreased vascular remodeling and fibrosis in the small vessels
- Mitigated inflammation & reduced small vessel thickness
- Significantly reduced inflammatory cytokines $\text{TNF}\alpha$, $\text{IL-}\beta$, IL-6 , and chemokine LTB_4

Brilaroxazine mitigates pulmonary hypertension and lung fibrosis/collagen



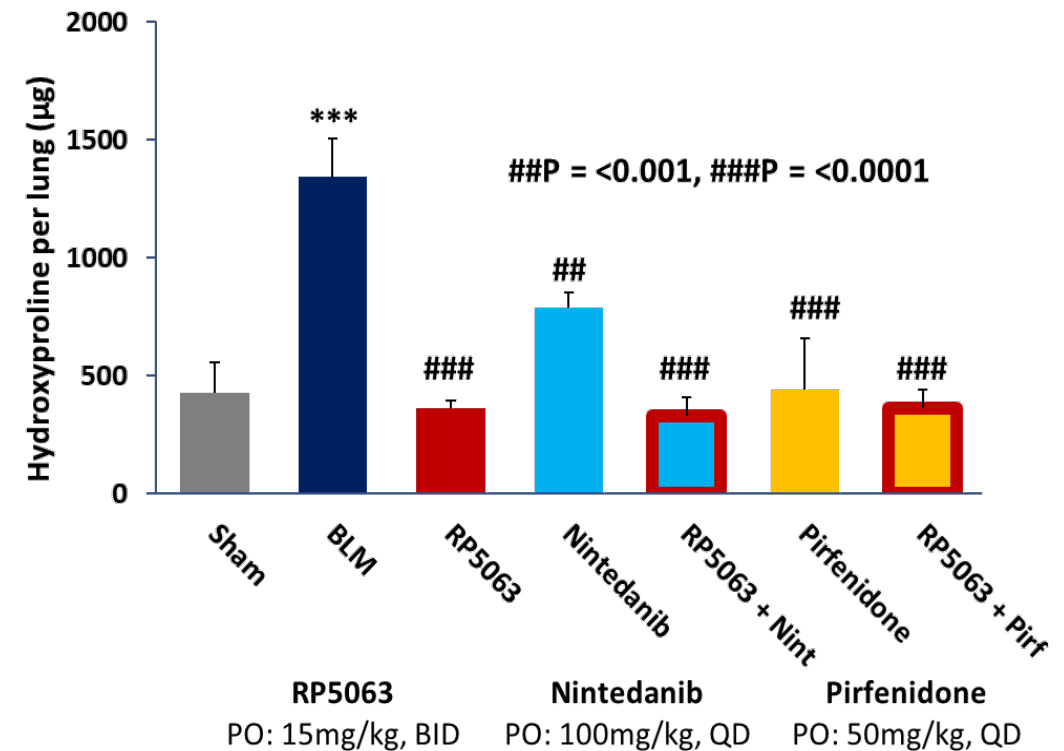
Brilaroxazine: Encouraging Results in Bleomycin-Induced IPF Rodent Model

Potential for Improved Treatment Effect Compared to Standard of Care

Brilaroxazine both alone and co-administered with standard of care for IPF

- Mitigated lung fibrosis and collagen deposits
- Decreased respiratory resistance & improved blood oxygen saturation
- Restored body weight and cardiac output
- Reduced the IPF biomarkers BALF cell counts, hydroxyproline, and blood lactate levels
- Decreased cytokines RANTES, IFN γ , MCP1, IL-6, and IL-17
- Improved survival rates

Brilaroxazine mitigates lung fibrosis / collagen (Decrease in Hydroxyproline)



Brilaroxazine: Ready for Phase 2 Trials in PAH and IPF

FDA granted Orphan Drug Designation

Brilaroxazine Phase 2 trials in PAH and IPF

- Preclinical evidence supports the use of Brilaroxazine in PAH and IPF
- Generally well-tolerated in clinical studies for schizophrenia in >250 patients
- Completed long-term regulatory toxicology studies
- Manufactured API and drug products (clinical trial materials)
- Oral once daily dosing, potential to develop once daily inhaler for enhanced effect and convenience

Key regulatory milestones achieved

- FDA reviewed preclinical pharmacology, toxicology, CMC, and clinical Phase 1 safety data for initiating a Phase 2 study
- FDA reviewed and provided guidance on Phase 2/3 clinical development plan and a potential “Disease Modifying Agent” label claim
- FDA granted Orphan Drug Designation for the treatment of PAH and IPF

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