



# REVIVA PHARMACEUTICALS HOLDINGS, INC. (NASDAQ: RVPH)

Corporate Presentation, October 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, 2023, 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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# 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 Q4 2024
- Topline readout expected in Q1 2026

Long-term clinical safety trial topline readout expected in Q1 2025

Potential NDA filing in Q2 2026

# Reviva Clinical Development Pipeline

			Discovery	Preclinical	Phase I	Phase II	Phase III	Est. Market Opportunity (\$B)
Brilaroxazine – Serotonin/ dopamine modulator (NCE)	Neuropsychiatric	Schizophrenia	[Progress bar]					\$13.4 <sup>(1)</sup>
		Bipolar Disorder	[Progress bar]					\$6.1 <sup>(2)</sup>
		Major Depressive Disorder	[Progress bar]					\$14.9 <sup>(3)</sup>
		Attention Deficit Hyperactivity Disorder	[Progress bar]					\$30.5 <sup>(4)</sup>
	Inflammatory	Pulmonary Arterial Hypertension	[Progress bar]					\$12.1 <sup>(5)</sup>
		Idiopathic Pulmonary Fibrosis	[Progress bar]					\$6.4 <sup>(6)</sup>
		Psoriasis (topical gel)	[Progress bar]					\$57.7 <sup>(7)</sup>
RP1208 – Triple reuptake inhibitor (NCE)	Depression	[Progress bar]					\$26.4 <sup>(8)</sup>	
	Obesity	[Progress bar]					\$77 <sup>(9)</sup>	

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

(1) By 2032 per Schizophrenia Market by Market Research Future 2024. (2) By 2028 per Bipolar Disorder Market by Skyquest Report 2022. (3) By 2032 per Major Depressive Disorder Market by Future Market Insights 2022. (4) By 2032 per ADHD market by Polaris Market Research 2023. (5) By 2032 per Pulmonary Arterial Hypertension (PAH) by Precedence Research 2023. (6) By 2031 per Idiopathic Pulmonary Fibrosis (IPF) by SkyQuest 2024. (7) By 2032 per Psoriasis Market by Precedence Research 2023. (8) By 2028 per Anxiety and Depression market, Report Linker 2023. (9) By 2030 per Morgan Stanley Research 2023

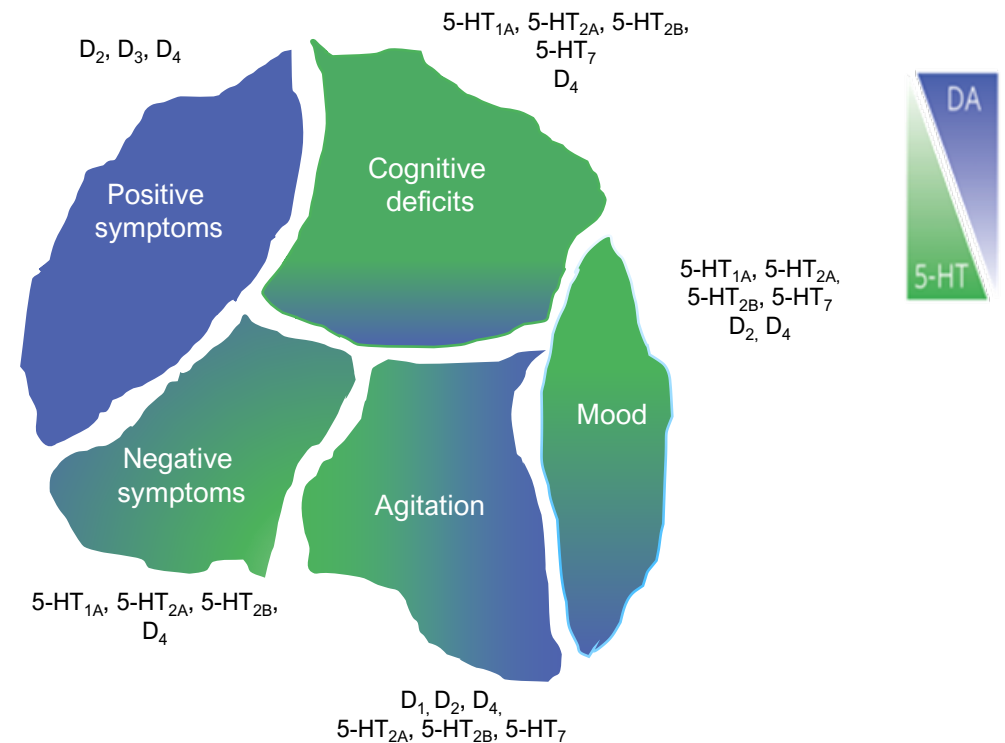


# Schizophrenia: Common Psychiatric Condition With Multiple Symptom Domains

Primarily driven by dysfunctional serotonin and dopamine signaling

- Affects ~1.1% of the world's population
  - ~ 24 million people globally
  - ~ 3.5 million people in USA
- Schizophrenia is not a single disease rather a mix of heterogenous psychotic symptoms with varying degrees of severity
- Most patients requires lifelong treatment
- ~30% of patients are treatment refractory
- Neuroinflammation is implicated as major contributing factor to schizophrenia
- Negative symptoms and nonadherence to treatment are the top unmet needs

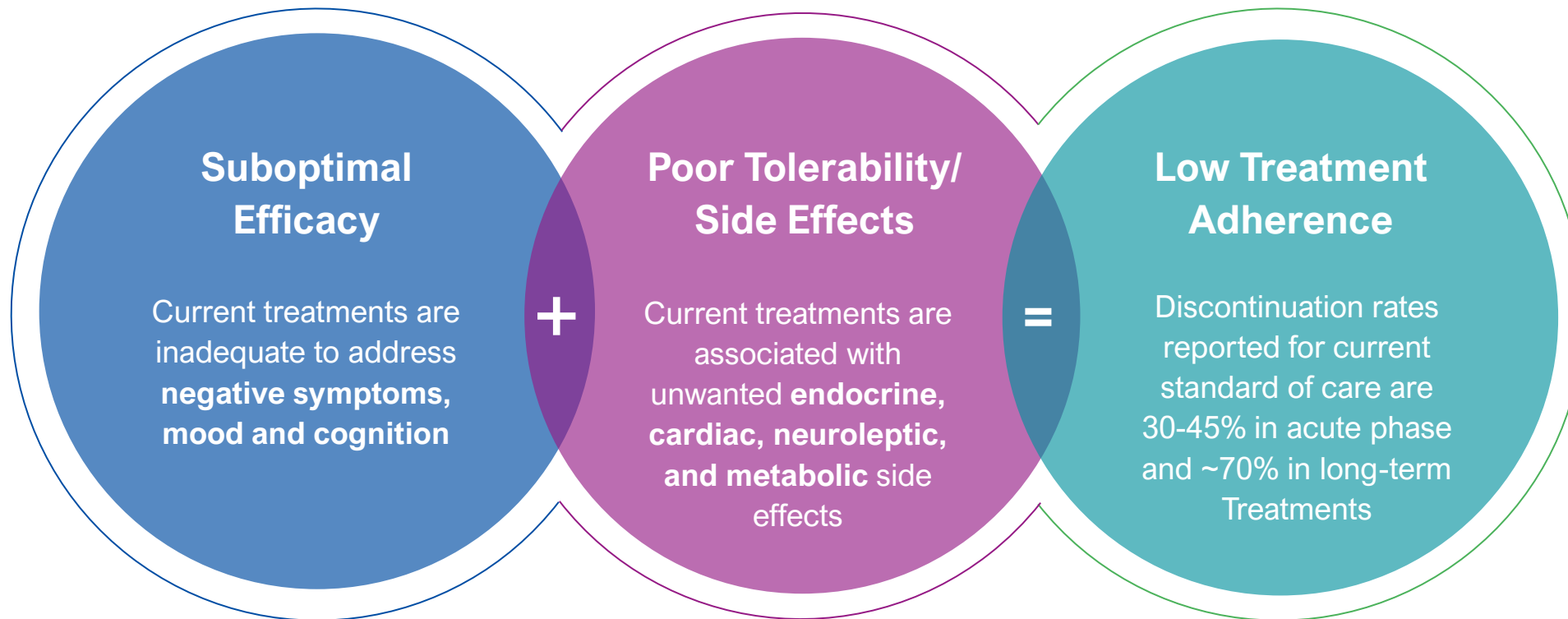
## Major Symptom Domains of Schizophrenia



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

# 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

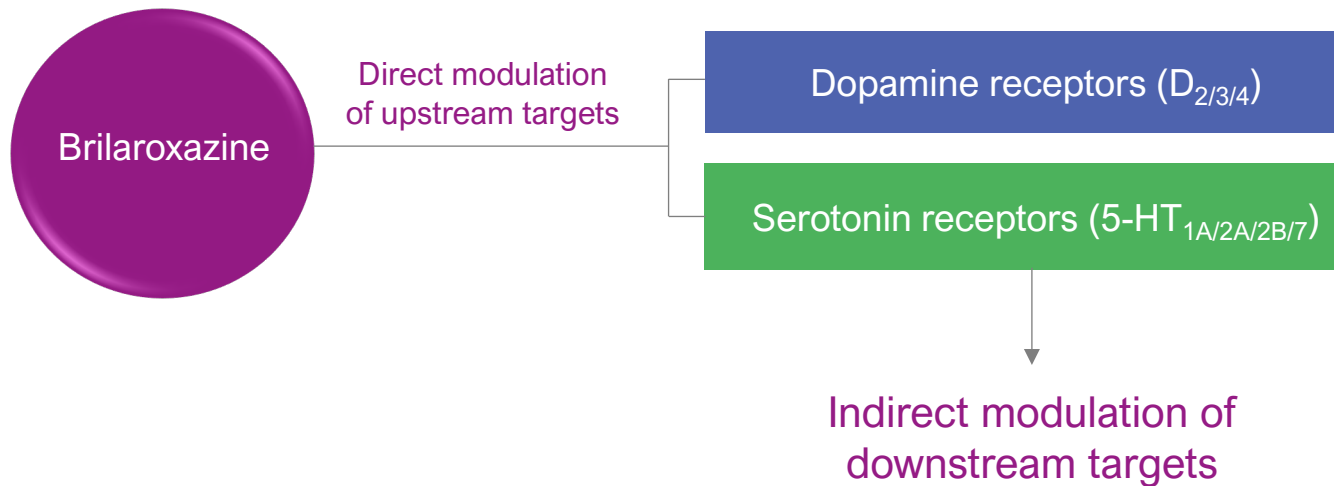
Statistically significant results on positive symptoms, negative symptoms and cognition factor

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

Discontinuation rate of 12-16% (lower than placebo) in acute phase treatment trials

# Brilaroxazine: Novel Serotonin Dopamine Signaling Modulator

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



Activity Level	Receptor	Ki (nM)
High (Ki, nM)* (5-HT <sub>2B</sub> > D <sub>2</sub> )	Dopamine D <sub>2</sub>	0.4
	Dopamine D <sub>3</sub>	3.7
	Dopamine D <sub>4</sub>	6
	Serotonin 5-HT <sub>1A</sub>	1.5
Moderate (Ki, nM)	Serotonin 5-HT <sub>2A</sub>	2.5
	Serotonin 5-HT <sub>2B</sub>	0.19
	Serotonin 5-HT <sub>7</sub>	2.7
	Nicotine α <sub>4</sub> β <sub>2</sub>	36.3
Weak or no significant activity	Serotonin 5-HT <sub>6</sub>	51
	No significant activities at therapeutic dose for off-targets 5-HT <sub>2C</sub> , α <sub>1,2</sub> , and M <sub>1-4</sub> implicated in cardiometabolic, metabolic, or GI side effects	

<p><b>Inflammatory cytokines</b></p> <p>Implicated in neuroinflammation</p>	<p><b>Nicotinic receptors</b></p> <p>Implicated in positive symptoms and cognition</p>	<p><b>NMDA/Glycine receptors</b></p> <p>Implicated in negative symptoms and cognition</p>	<p><b>GABA receptors</b></p> <p>Implicated in mood</p>
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A photograph of a doctor in a white lab coat and blue scrubs, holding a large X-ray of a human torso. The doctor has a stethoscope around their neck. The image is partially obscured by a blue diagonal line and a white rounded rectangle containing the text.

## 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
<p>✓</p> <p><b>N = 234 (4-week)</b> <b>Acute schizophrenia or schizoaffective disorder</b></p>	<p>✓</p> <p><b>N = 411 (4-week)</b> <b>Acute schizophrenia</b></p>	<p><b>N = 100 completers (1-year)</b> <b>Stable schizophrenia</b></p>	<p><b>N = 450 (4-week)</b> <b>Acute schizophrenia</b></p>
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 in the End-of-Phase 2 (EOP2) meeting	Completed with topline results announced in October 2023	Topline data expected in Q1 2025	Expected initiation in Q4 2024; Topline readout expected in Q1-2026

Registrational Phase 3 RECOVER-2 trial will replicate the successful trial design of Phase 3 RECOVER-1 trial, replacing the low dose with 30 mg

***Most non-clinical development is complete, and NDA filing is planned for Q2 2026***

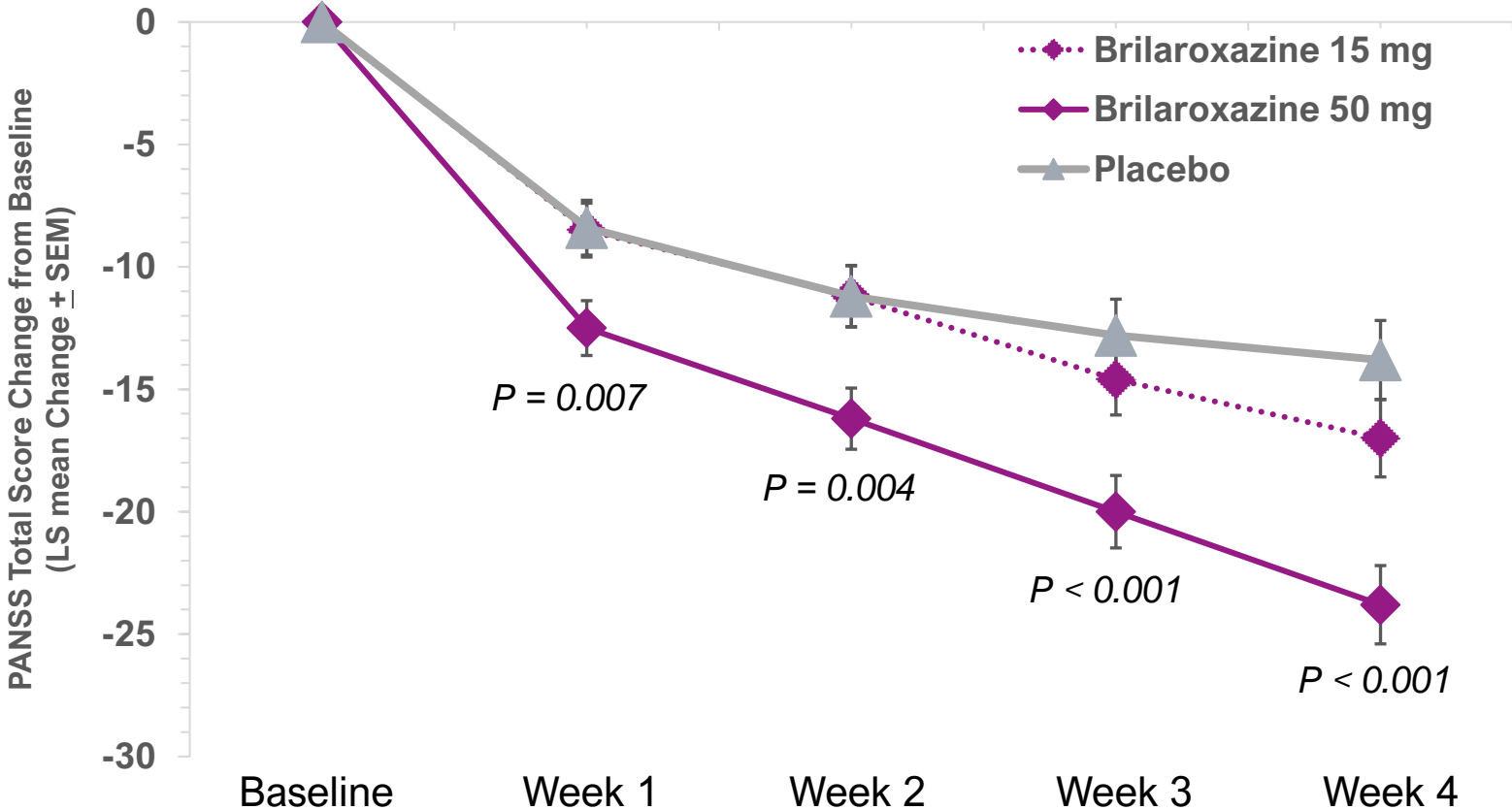
# RECOVER-1 Trial Primary Endpoint: PANSS Total Score

10.1-point reduction in PANSS total score vs. placebo,  $p < 0.001$  (-23.9 brilaroxazine 50 mg vs. -13.8 placebo)

## PANSS Total Score

- Successfully met PANSS Total Score primary endpoint for brilaroxazine 50 mg
- Separation for brilaroxazine 50 mg from placebo within a week
- Brilaroxazine 15 mg numerically separated from placebo
- No significant difference in treatment effect between the US and ex-US patients
- Results further supported by biomarker data

Cohen's d effect size of 0.6

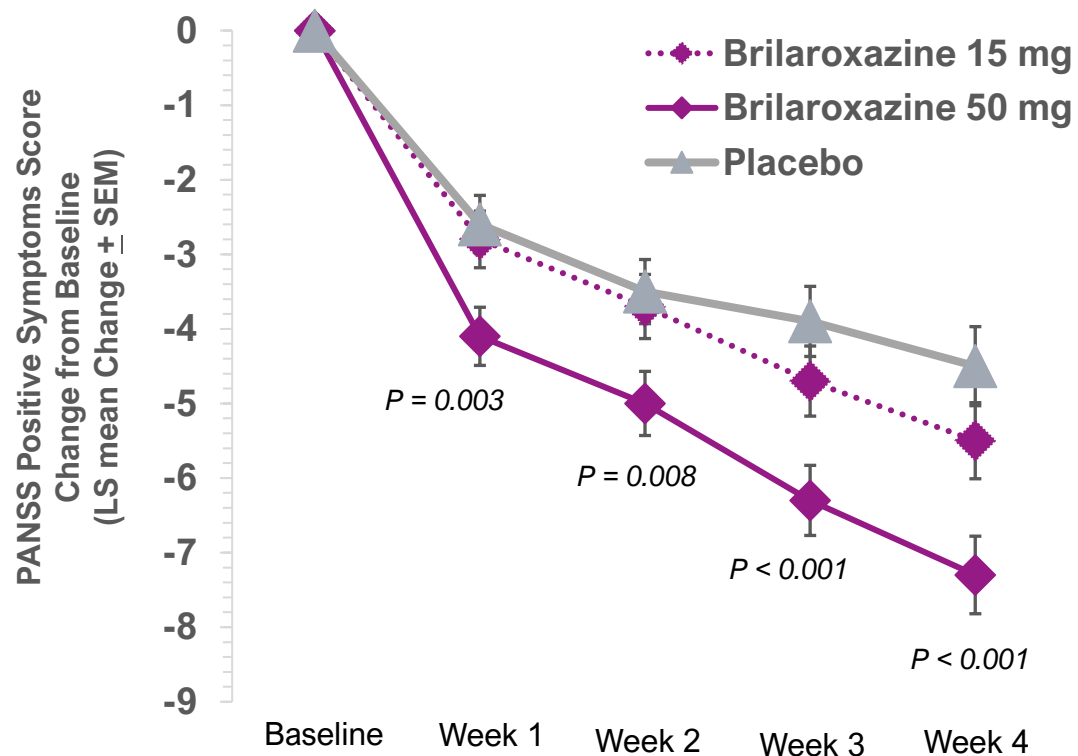


# RECOVER-1: Efficacy Endpoints Positive Symptoms and Agitation/Excitement

Significant decrease in positive symptoms & agitation/excitement in brilaroxazine 50 mg vs. placebo

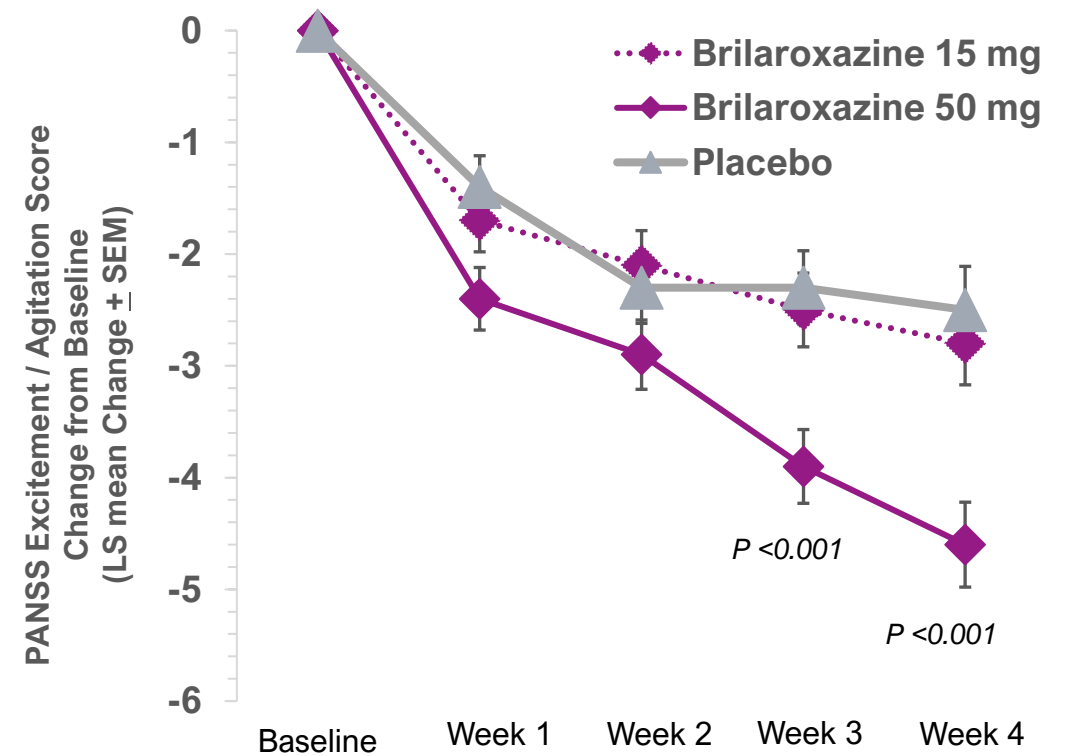
## Decrease in Positive Symptoms

Cohen's d effect size of 0.5



## Decrease in Agitation/Excitement Symptoms

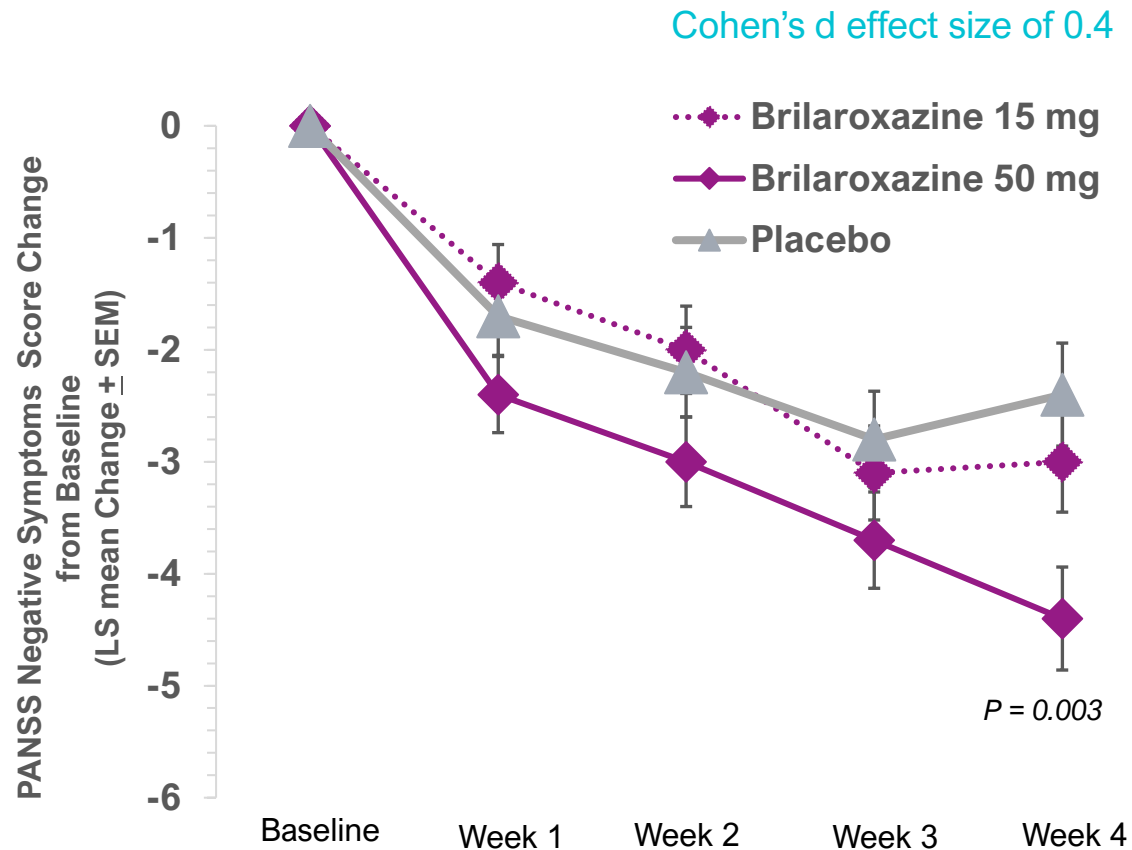
Cohen's d effect size of 0.5



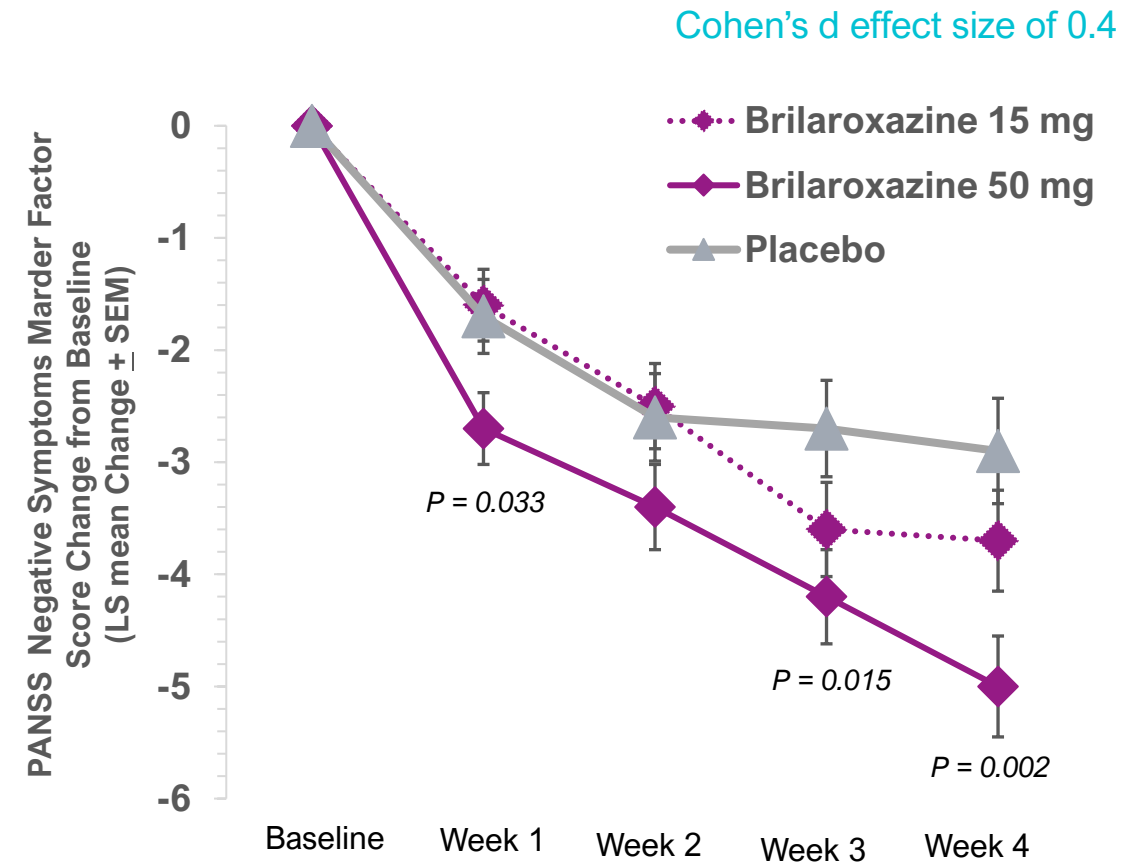
# RECOVER-1: Efficacy Endpoint Negative Symptoms

Significant reduction in negative symptoms in brilaroxazine 50 mg vs. placebo

## Decrease in Negative Symptoms



## Decrease in Negative Symptoms (Marder Factor)

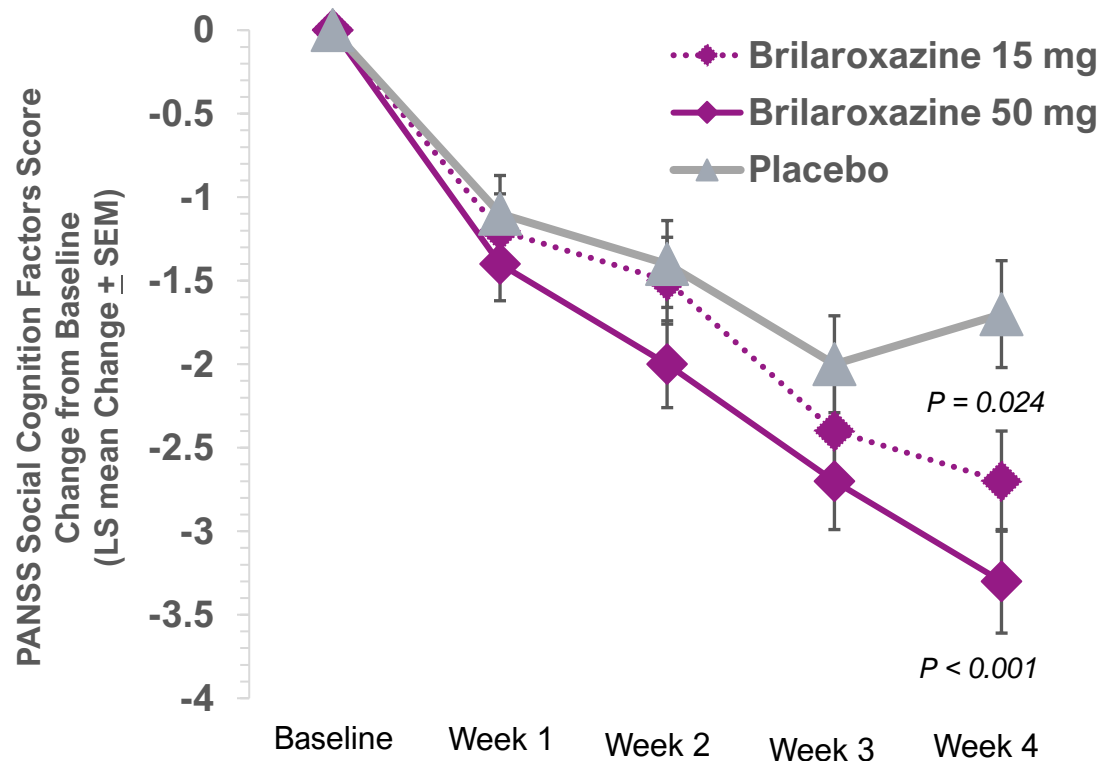


# RECOVER 1: Efficacy Endpoints Social Cognition and Social Functioning

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

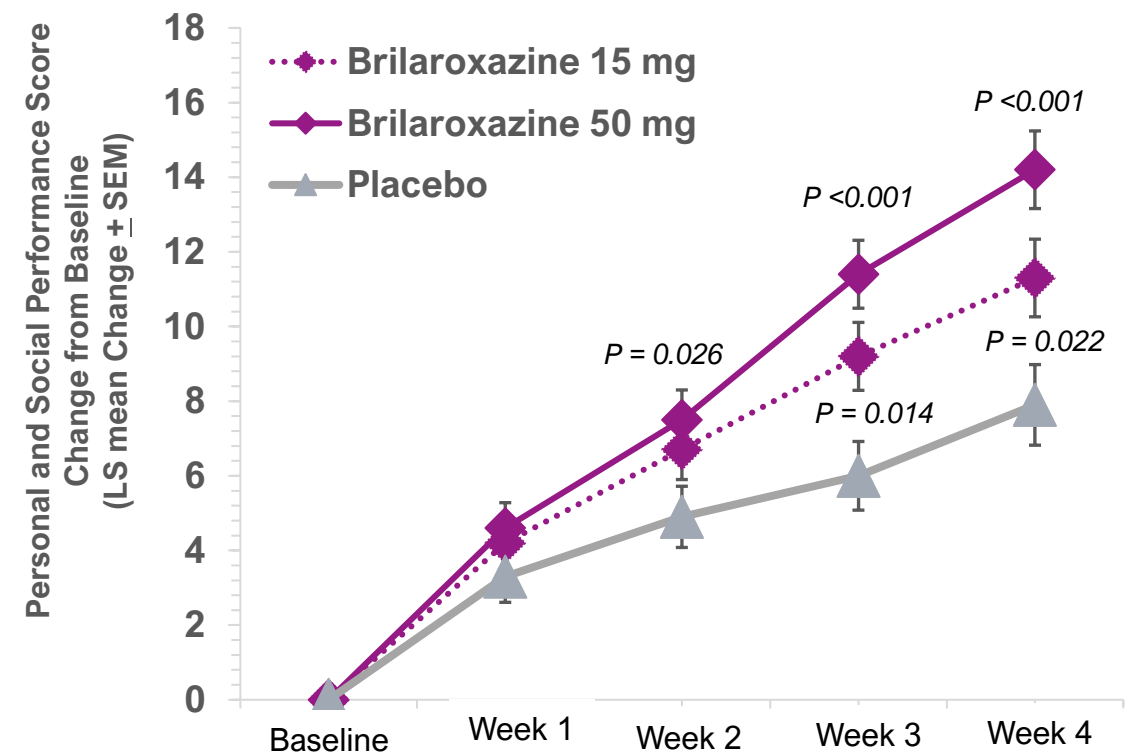
## Decrease in Social Cognition Deficits

Cohen's d effect size of 0.5



## Improvement in Personal & Social Performance

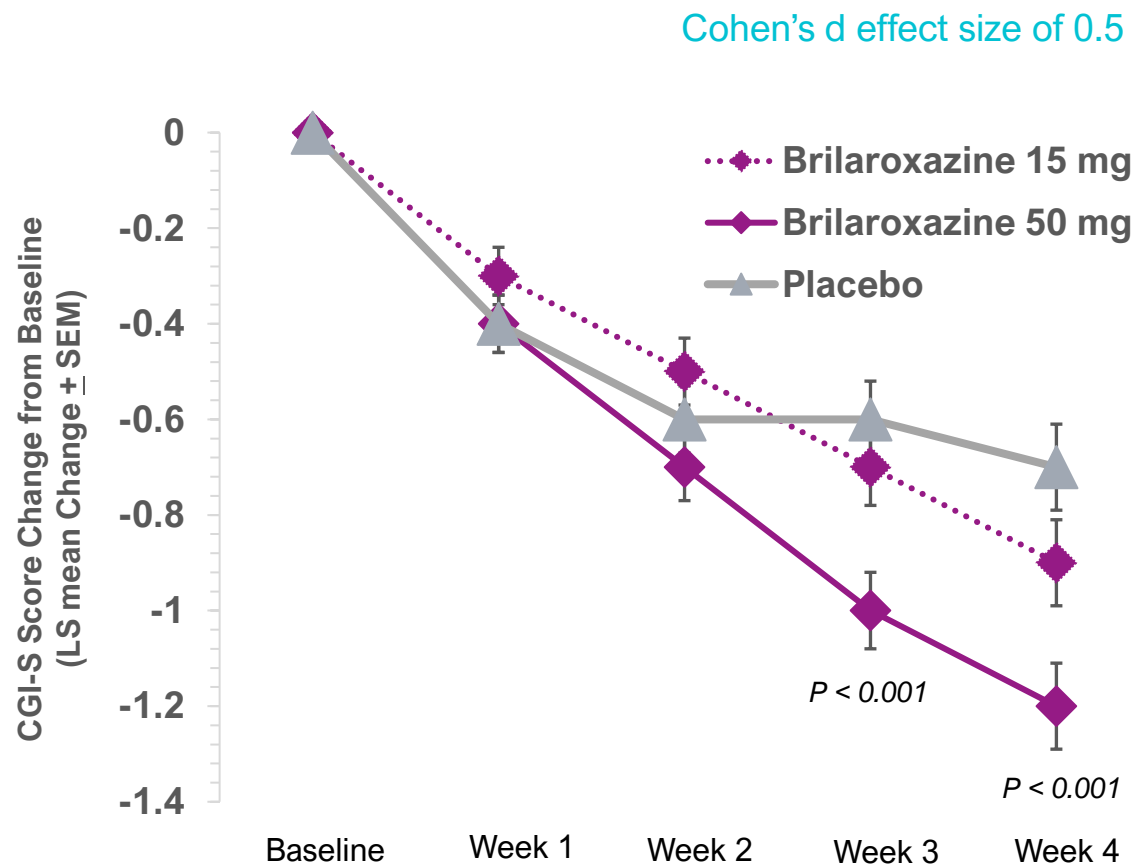
Cohen's d effect size of 0.5



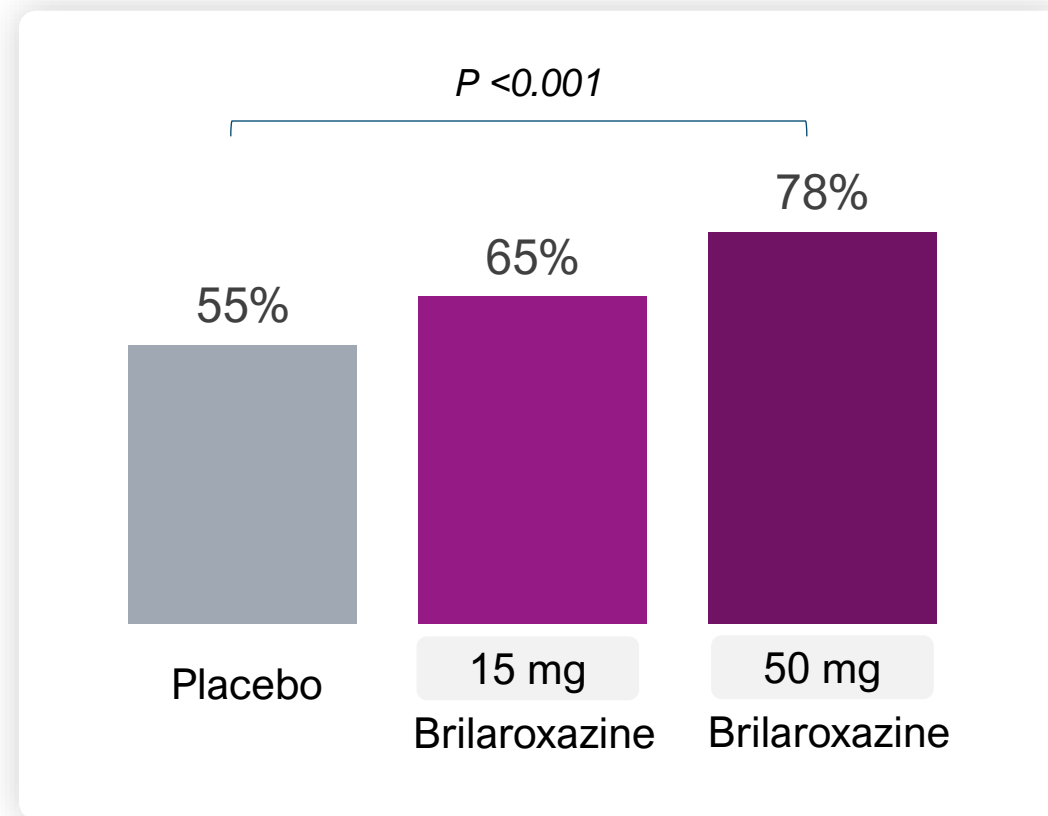
# RECOVER-1: Efficacy Endpoint CGI-S Scores

≥1-Point reduction in CGI-S score in brilaroxazine 50 mg vs. placebo

## CGI-S Score ≥ 1-Point Reduction



## Proportion of Subjects with ≥ 1-Point Reduction

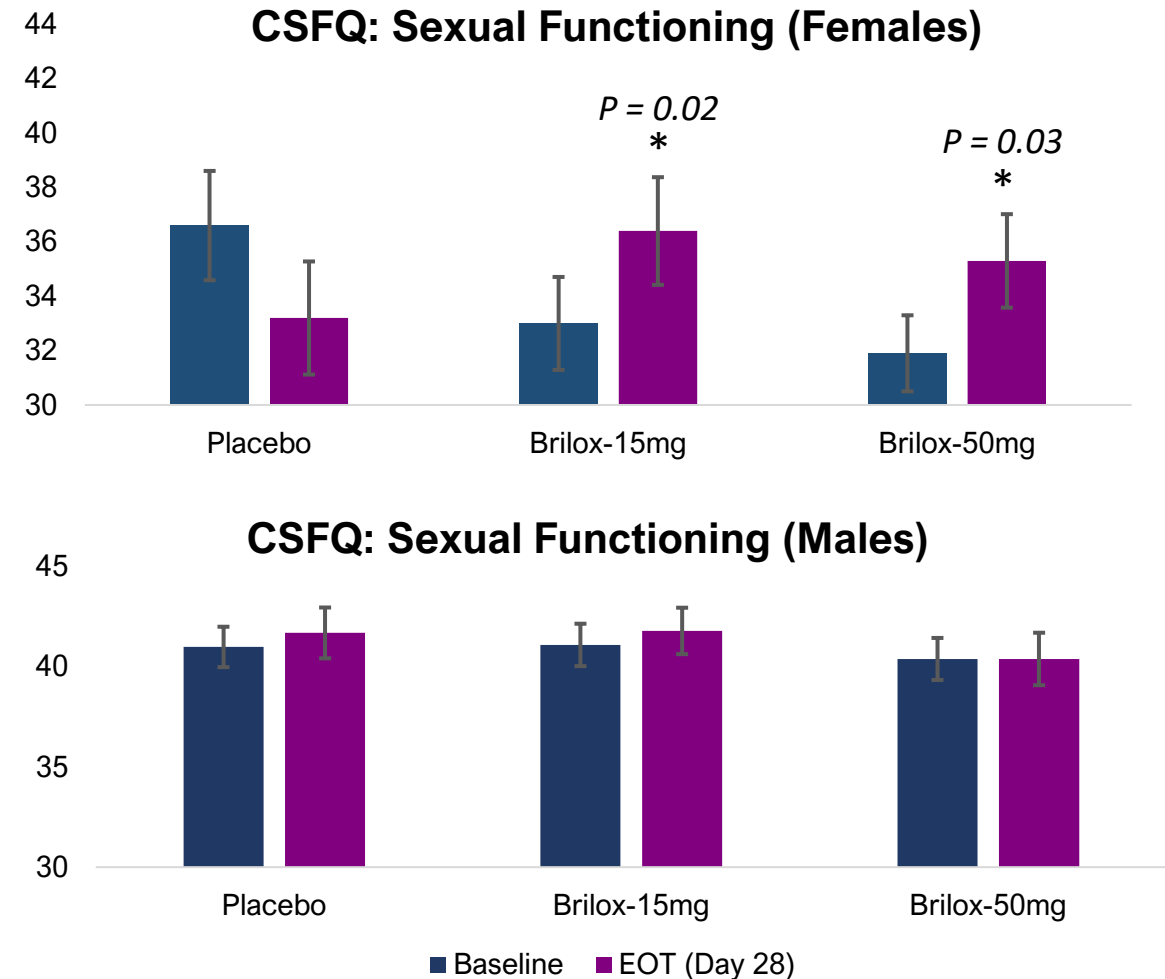


# Efficacy & Safety Surrogate Outcome: CSFQ Score Changes for Sexual Functioning

## RECOVER-1: 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  $\leq 41$  for females and  $\leq 47$  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



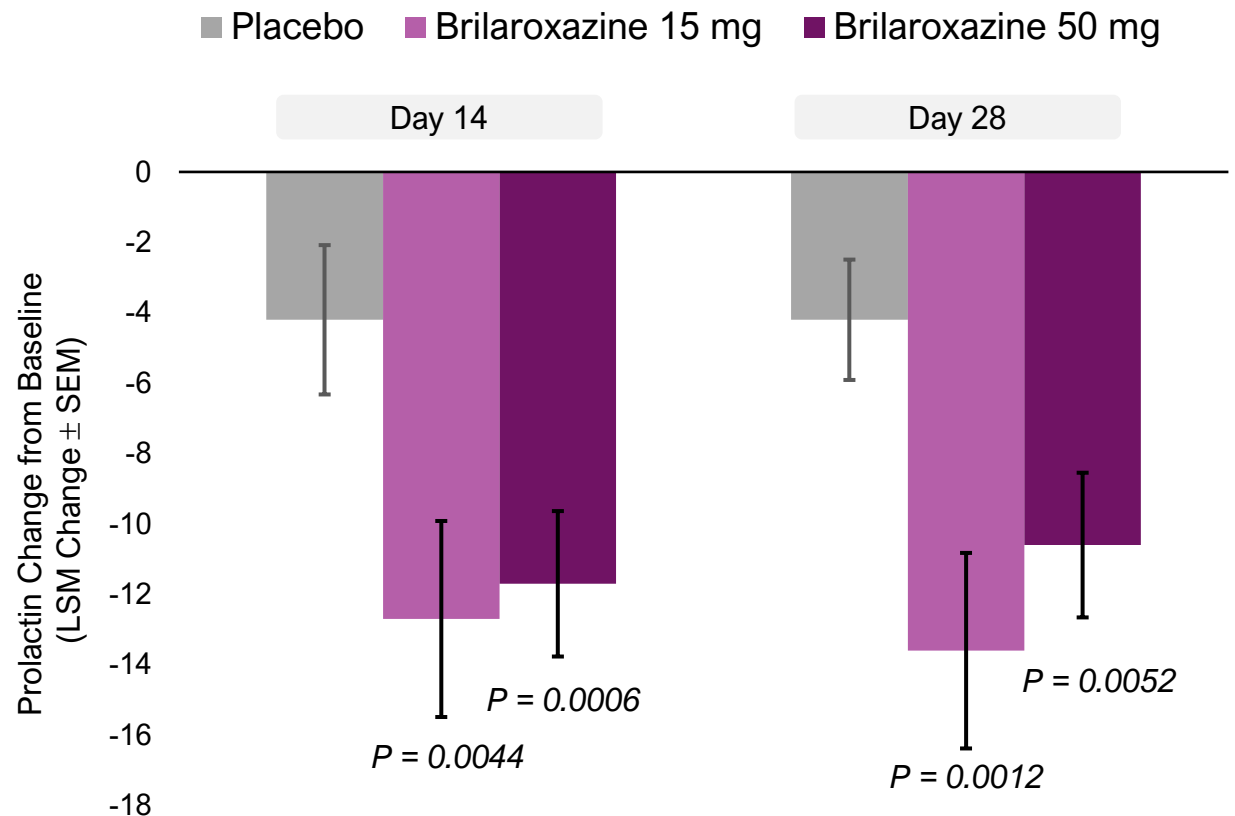
# Efficacy & Safety Biomarker: Change in Prolactin Hormone

RECOVER-1: 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 associated 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.

## Change in Serum Prolactin (ng/mL)





# Efficacy & Safety Biomarker: Change in Brain-Derived Neurotrophic Factor (BDNF)

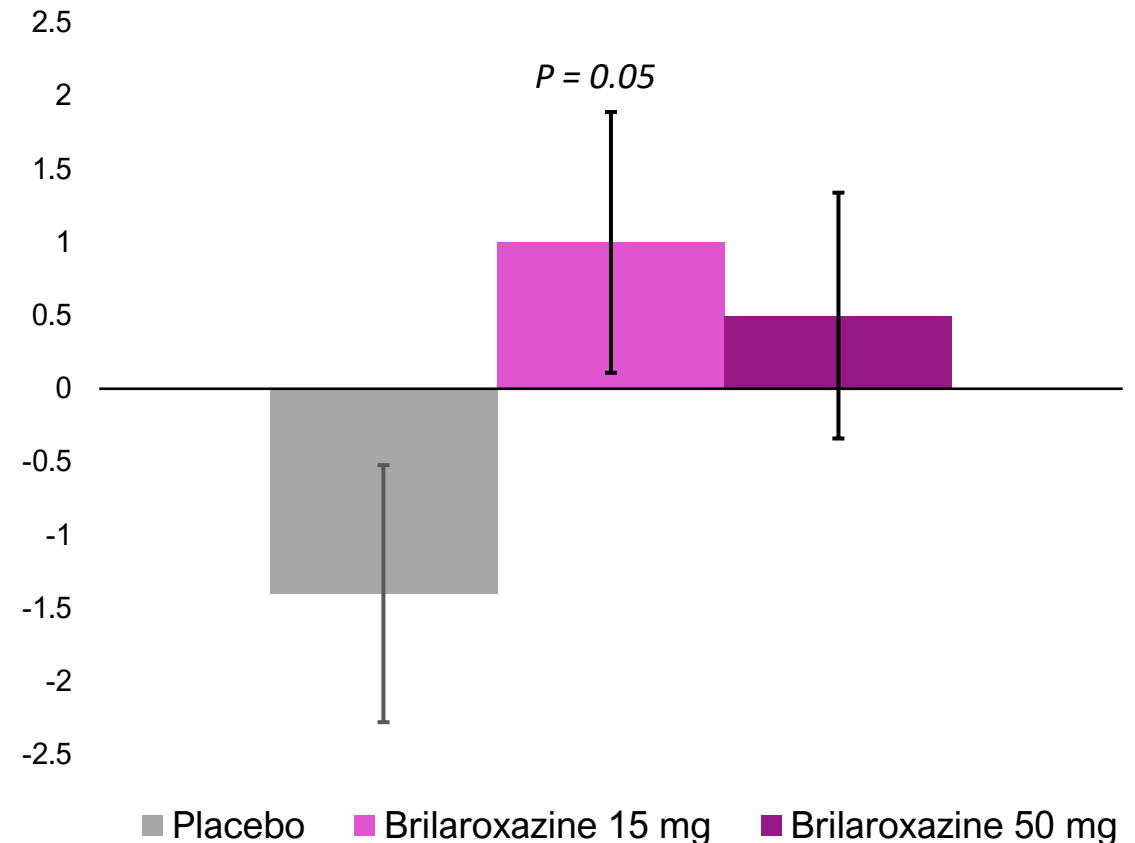
## RECOVER-1: Clinically significant improvement in BDNF levels with brilaroxazine 15 mg vs placebo

### 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

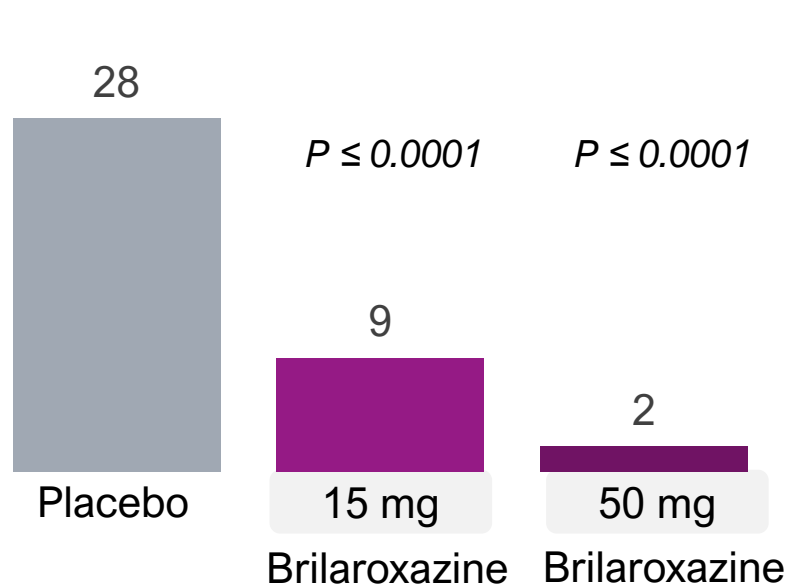
### Improvement in Serum BDNF (ng/mL)



# Efficacy & Safety Biomarkers: Change in Serum Cytokines & Chemokines

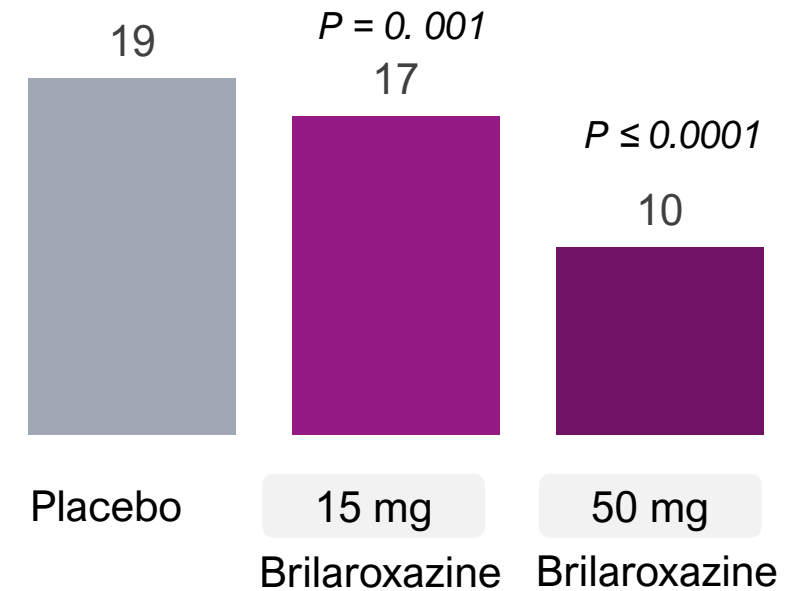
RECOVER-1: Significant decrease in cytokine IL-8 and chemokine MIP-1 in brilaroxazine vs placebo

### 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

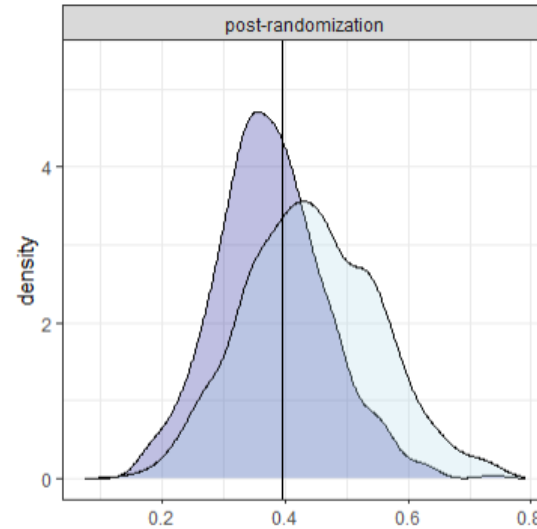
(Frydecka D et al. Brain Behavior and immunity 2018,; Hong S et al Schizophrenia Res 2016)

Brilaroxazine showed decrease in IL-6 and IFN- $\gamma$  inducible protein IP-10, and increase in IL-10 versus placebo

# Vocal Biomarker (VBM) Speech Latency Heterogeneity<sup>1</sup> in RECOVER-1 Trial

Speech Latency is highly heterogeneous across patients | Did their treatment responses differ?

VBM positive patients have Prominent Negative Symptoms (PNS)<sup>2,3,4</sup>



Machine Learning [of post-randomization data] identifies:

❑ **Vocal Biomarker (VBM) Positive** (@ baseline, N = 220)

- Slow responses
- **More severe negative symptoms (d = 0.95)**
- Slightly Younger (d = 0.57), but similar in sex.

❑ **Vocal Biomarker (VBM) Negative** (@ baseline, N = 187)

- Fast responses
- **More severe positive symptoms (d = 0.31)**

(1) Schizophrenia is a mix of heterogeneous psychotic symptoms with varying degrees of severity. (2) PNS = Negative symptoms that are present at a predefined level of severity, regardless of the severity of other symptoms.

(3) FDA Public Meeting on Evaluating the Negative Symptoms of Schizophrenia in Clinical trials, August 16, 2024; (4) Harvey PD et al Schizophrenia research 2024, 271:246-252

# Brilaroxazine Key Points of Clinical Differentiation Supported by Biomarkers

Favorable efficacy, safety and treatment adherence profile in brilaroxazine 50mg vs placebo

## Significant Change in Blood Biomarkers Patients (N=411, ITT)

**BDNF** ↑

**Hormones:**

Prolactin ↓

Thyroid T3 ↑

**Cytokines:**

IL-8 ↓

IL-10 ↑

IP-10 ↓

MIP-1 ↓

## Significant Treatment Effects on Major Symptom Domains & Unmet Needs in all Patients (N = 411, ITT)

**Primary Endpoint:**

10.1-point (ES: 0.6) ↓ in PANSS total score

**Secondary Endpoints:**

2.4-point (ES: 0.5) ↓ in positive symptoms

2-point (ES: 0.4) ↓ in negative symptoms

1.6-point (ES: 0.5) ↑ in social cognition

6.1-point (ES:0.5) ↑ in function (PSP)

2.1-point (ES: 0.5) ↓ in agitation/excitement

≥1-point (ES: 0.5) ↓ in CGI score in 78% patients

**Treatment Adherence**

16% Discontinuation in brilaroxazine vs 22% in placebo

## Digital Biomarker, VBM Prominent Negative Symptoms Patients (N=220, VBM Positive)

**Primary Endpoint\*:**

15-point (ES: 0.9) ↓ in PANSS total score

**Secondary Endpoints\*:**

3.5-point (ES: 0.8) ↓ in positive symptoms

3.7-point (ES: 0.6) ↓ in negative symptoms

3.8-point (ES: 0.8) ↑ in social cognition

≥1-point (ES: 0.7) ↓ in CGI score

**\*Greater effect size and statistically improvements in efficacy outcomes**

# Brilaroxazine Phase 3 RECOVER Trial: Safety, Tolerability and Compliance

Variables	Brilaroxazine 15 mg (N=140)	Brilaroxazine 50 mg (N=134)	Placebo (N=137)
<b>Any Treatment Emergent Adverse Event (TEAE)</b>	104 (34.5%)	107 (35.5%)	90 (29.9%)
<b>Serious Adverse Events possibly related to Brilaroxazine</b>	1	0	N/A
<b>Discontinuation<sup>1</sup>, n (%)</b>	26 (18.6%)	22 (16.4%)	30 (21.9%)
TEAE occurring in >5% participants			
Somnolence	4 (3.8%)	11 (10.2%)	3 (3.3%)
Headache	8 (7.6%)	8 (7.4%)	3 (3.3%)
<b>Metabolic Changes (weight and lipids), TEAE</b>			
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 (%)	4 (2.8)	9 (6.7)	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)
<b>Extrapyramidal Symptoms, TEAE</b>			
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)

(1) Brilarox-15 mg had 1 (0.71%) TEAE related discontinuation;

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

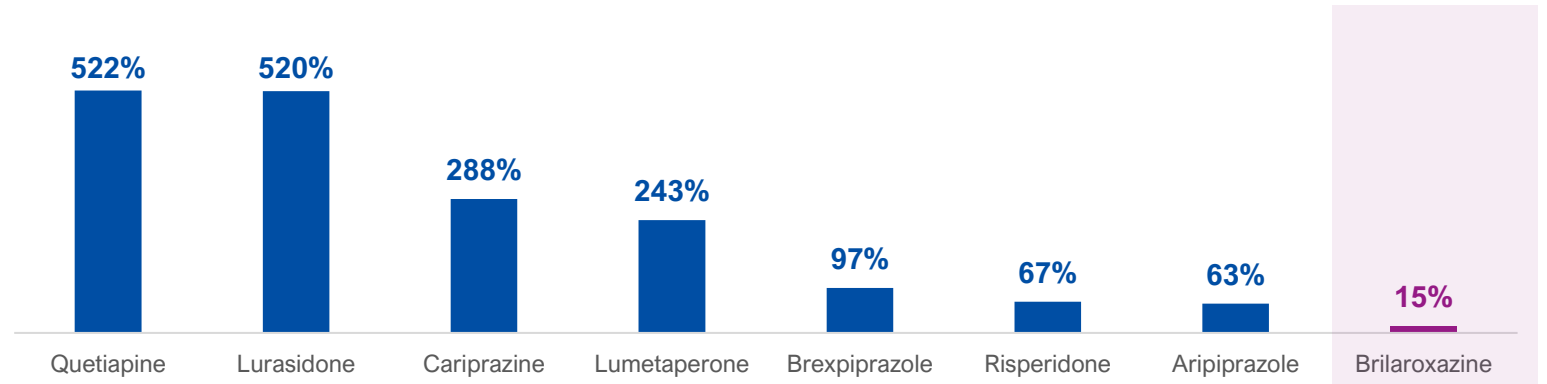
DDIs and polypharmacy alter plasma drug concentrations, and can impact efficacy and side effect profiles of a drug<sup>11</sup>

~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

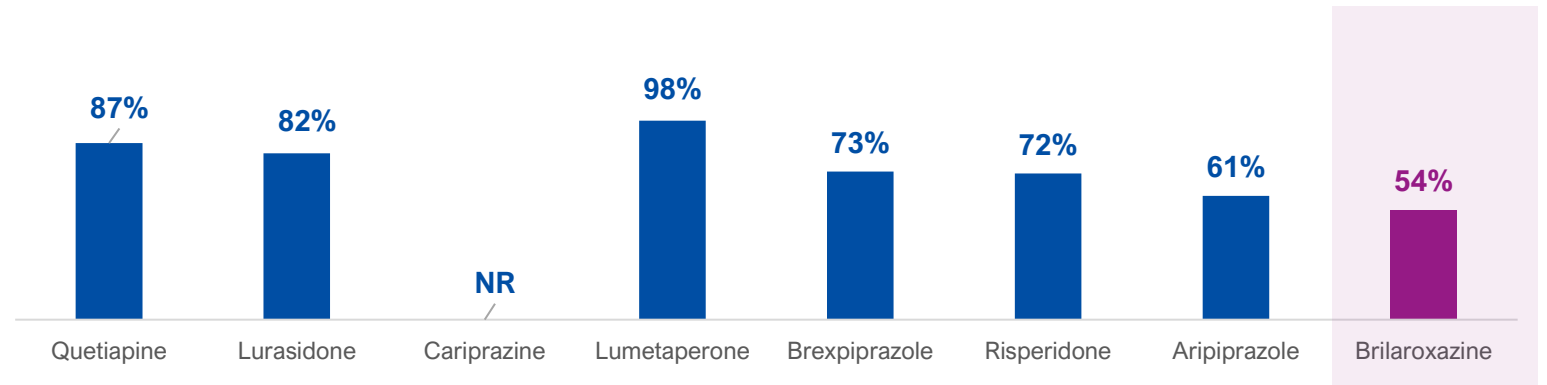
## Change in drug concentration with a CYP3A4 Inhibitor

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

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



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



↑ Lower is better  
↓

\*Olanzapine<sup>9</sup> not evaluated; metabolized by CYP1A2<sup>10</sup>

(1) Bhat L et al, ASPET 2023 (poster #376); (2) Aripiprazole (Abilify) NDA document, 2001; (3) Mahatthanatrakul et al, J Clin Pharm Thera 2007, 32(2):161-167 ; (4) Brexpiprazole (Rexulti) NDA document, 2014; (5) Lumetaperone (Caplyta) NDA document, 2018; (6) Cariprazine (Vraylar) NDA document 2014; (7) Pharmaceuticals 2020; (8) Quetiapine (Seroquel); Grim et al., Brit J Clin Pharm 2005, 61(1):58-69; (9) Olanzapine NDA document; (10) Vilckova et al., Onco Lett 2023, 25:85; (11) Bole B et al, Medicina 2023, 59:284. NR: not reported

# 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
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### 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	Improvement $\geq$ 1, 78% P<0.001 (Effect Size, 0.5)	Improvement $\geq$ 1, 72% P=0.02

### 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)

# RECOVER-1 Trial Conclusions: Treatment Effect on Schizophrenia

Brilaroxazine demonstrates high efficacy across multiple symptom domains with strong treatment adherence

## Consistent, Wide-Spectrum Efficacy

Brilaroxazine was consistent across multiple domains associated with schizophrenia, from positive and negative symptoms to social functioning and quality of life

## Well-Conducted Trial, High-Quality Data

Data quality was continuously monitored by an independent CRO utilizing validated methods to reduce error and placebo response via standardized training & calibration of the PANSS and blinded monitoring of clinician and site performance

## Strong Efficacy/ Side-Effect Ratio

Compared to existing marketed drugs, brilaroxazine shows significant wide-spectrum efficacy across primary and secondary endpoints with high levels of treatment adherence

## Potential to Significantly Impact Unmet Needs

Brilaroxazine may address many unmet needs in both acute and chronic phases of schizophrenia which are critical to functional recovery across the lifespan

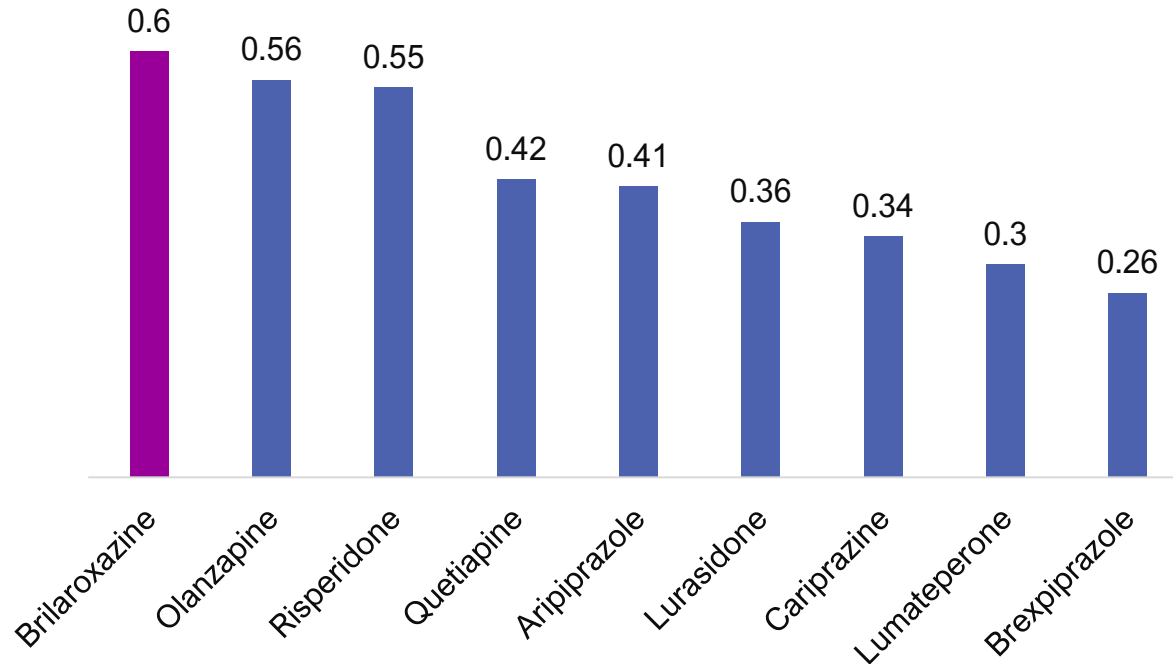
Objective vocal biomarker data confirms significant impact of brilaroxazine on negative symptoms and other major symptom domains of schizophrenia



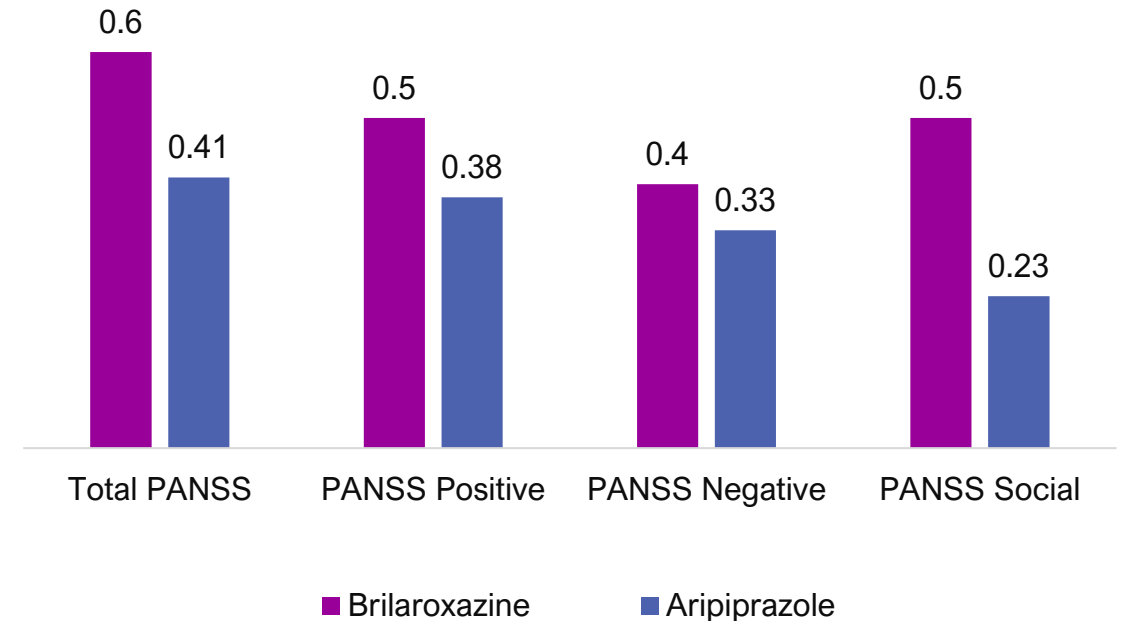
# Comparison of Treatment Effect Size from Phase 3 Studies

Primary endpoints and major secondary efficacy endpoints

## Brilaroxazine<sup>1</sup> vs Marketed Antipsychotics<sup>2,3</sup>



## Brilaroxazine<sup>1</sup> vs Aripiprazole<sup>2</sup>



Source: (1) Bhat L et al ASCPT 2024 (Poster #LB008) and SIRS 2024 (Poster #T291); (2) Huhn M et al. Lancet 2019, 394:939-951; (3) Correll CU et al. JAMA Psychiatry 2020, 77(4):349-358

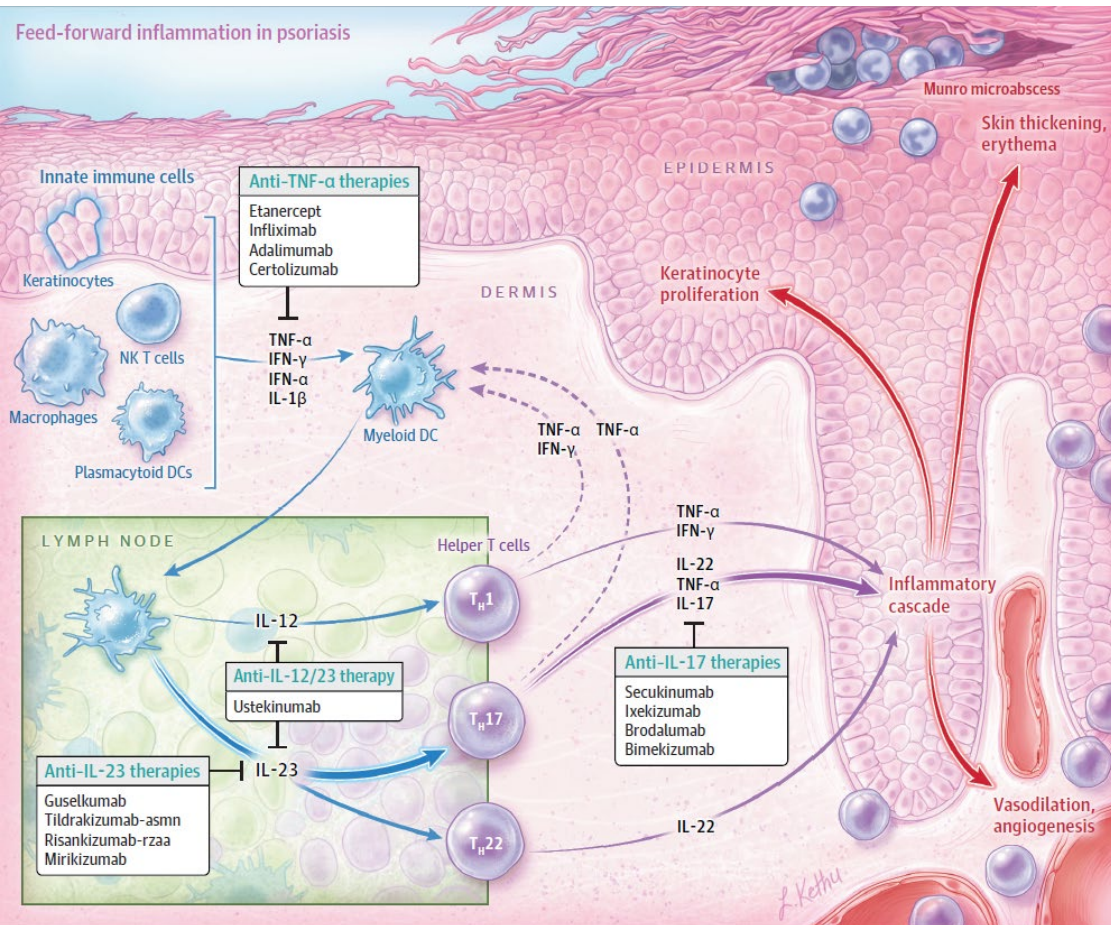


## Inflammatory / Immune Disease Programs

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

# Brilaroxazine has Potential to Treat Psoriasis

Inflammatory skin disease driven by dysfunctional serotonin-dopamine signaling

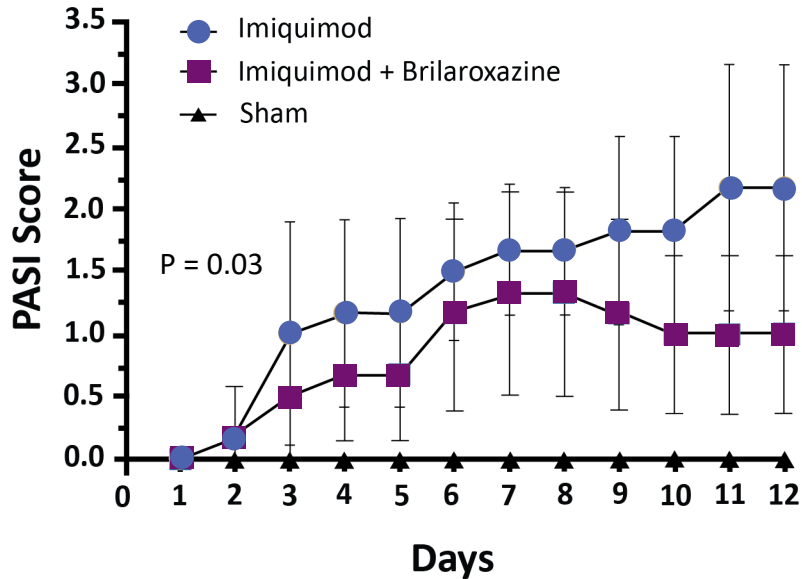


- Approx 3% of the US population and an estimated 125 million people worldwide suffer from psoriasis
- An estimated one-third of neuropsychiatric and neurodegenerative disease patients suffer from psoriasis
- Currently there is no cure for psoriasis
  - Topical corticosteroids therapies remain the cornerstone 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

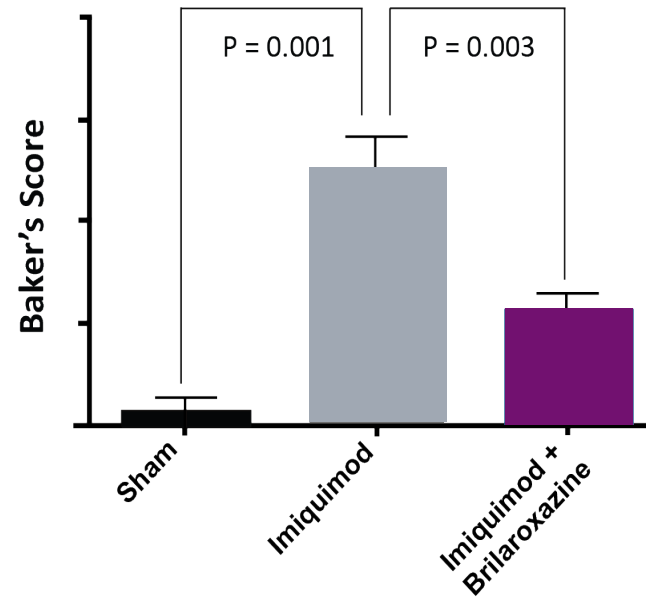
# Brilaroxazine Demonstrated Encouraging Preclinical Efficacy

In an imiquimod induced mouse model of psoriasis

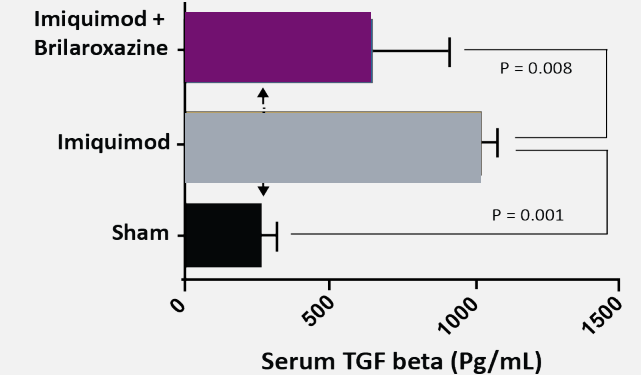
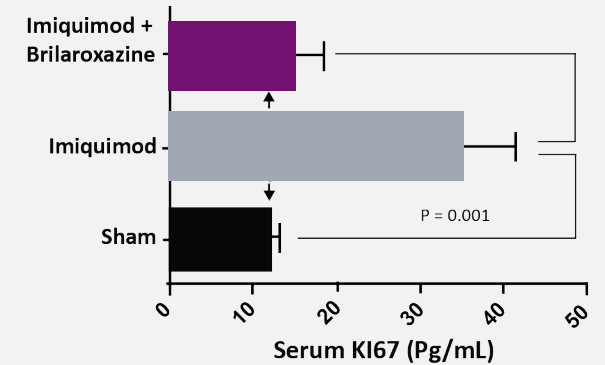
## Psoriasis Area Severity Index (PASI)



## Psoriasis Severity by Baker Score



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



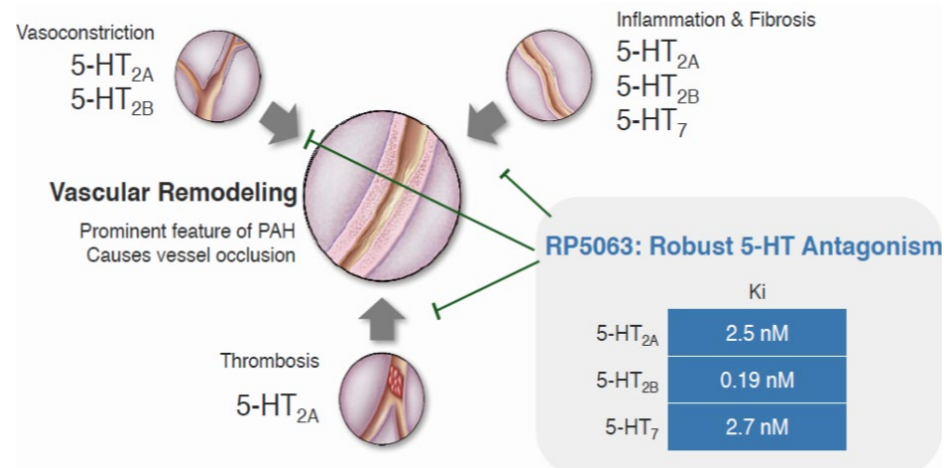
**Brilaroxazine topical liposomal gel significantly decreased**

- 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

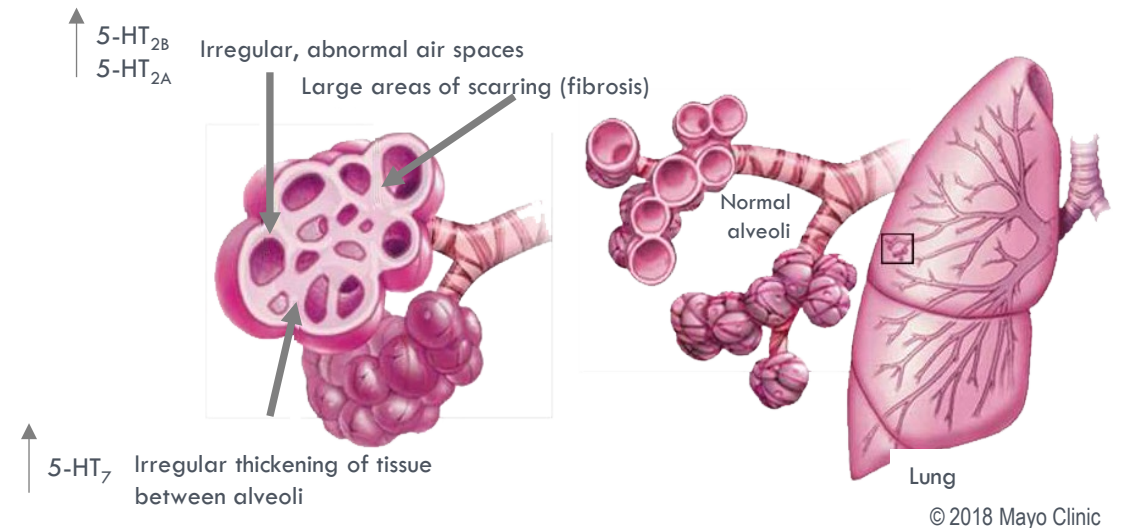
PAH and IPF are Orphan Diseases that involve dysfunctional serotonin signaling

## 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<sub>2A/2B/7</sub> 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

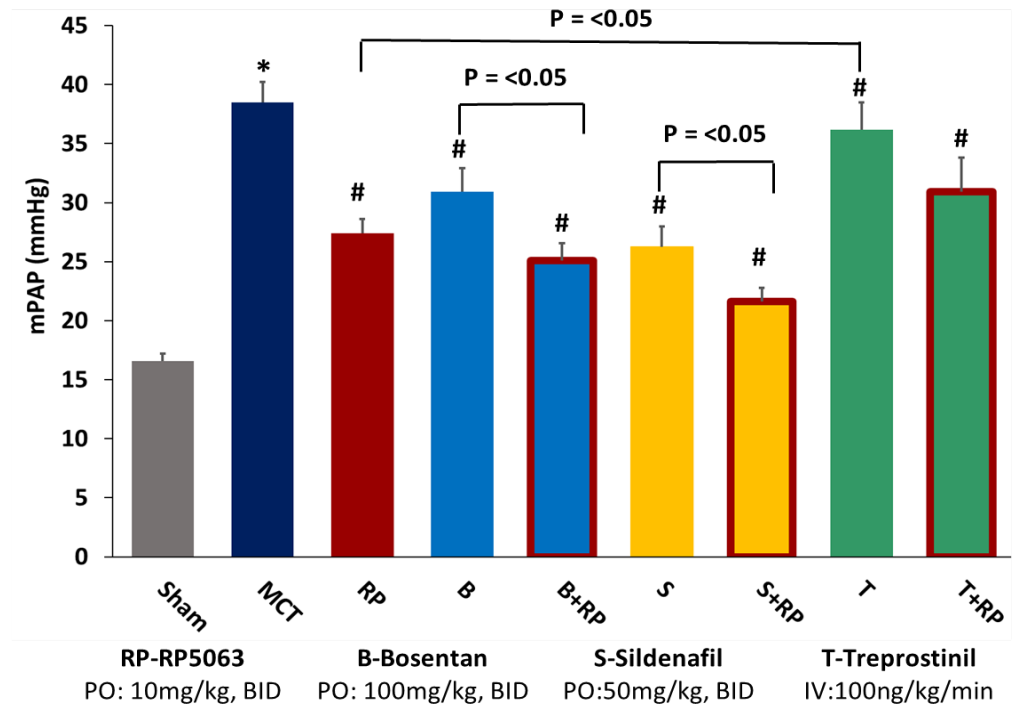
# Brilaroxazine: Encouraging Results in PAH Translational Rodent Models

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  $TNF\alpha$ ,  $IL-\beta$ ,  $IL-6$ , and chemokine  $LTB4$

## Brilaroxazine mitigates pulmonary hypertension and lung fibrosis/collagen



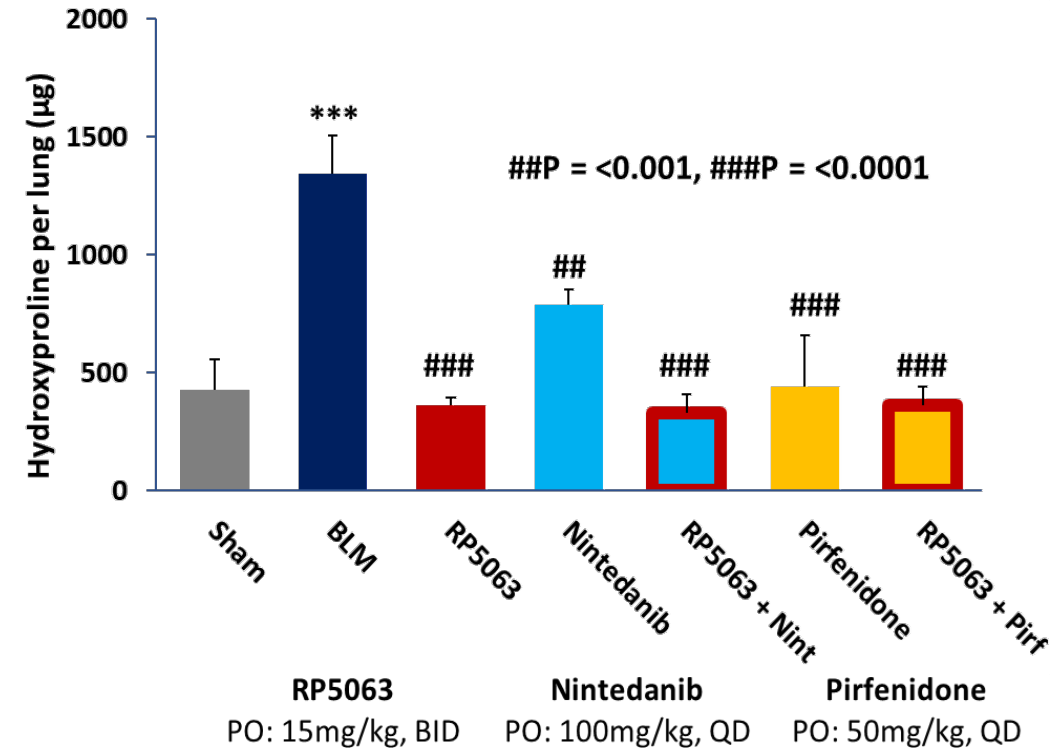
# Brilaroxazine: Encouraging Results in Bleomycin-Induced IPF Rodent Model

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,  $IFN\gamma$ , 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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