



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

Corporate Presentation, July 2023



# 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 RECOVER Phase 3 trial and timing of topline data, 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, trial results, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth and financing 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, including the potential impact of the COVID19 pandemic and the potential impact of sustained social distancing efforts, 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. 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.

# Key Business Highlights

## Company Overview



Late-stage pharmaceutical company developing new therapies for central nervous system, inflammatory, and cardiometabolic diseases

Chemical genomics driven discovery approach

Strong patent portfolio

## Lead Asset: Brilaroxazine



Differentiated pharmacology profile as modulator of serotonin and dopamine signaling pathways

Prioritizing ongoing pivotal Phase 3 trial in schizophrenia with topline data anticipated in Q3 2023

Potential for clinical expansion in additional neuropsychiatric and inflammatory diseases

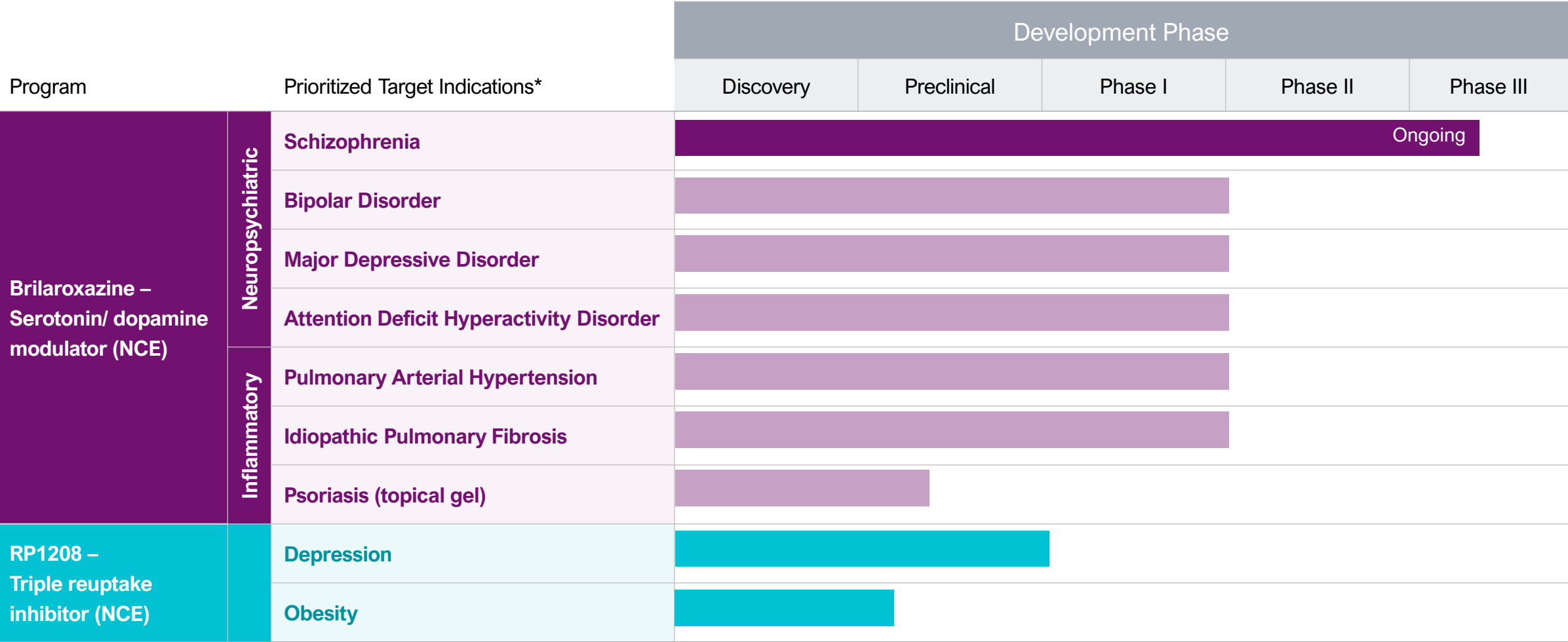
## Market Opportunity



Global addressable market size for brilaroxazine:

\$10.1 B for schizophrenia by 2028<sup>1</sup>  
\$6.2 B for bipolar disorder by 2027<sup>2</sup>  
\$24.5 B for MDD by 2030<sup>3</sup>  
\$29.3 B for ADHD by 2028<sup>4</sup>  
\$51.2 B for psoriasis by 2030<sup>5</sup>  
\$11.0 B for PAH by 2030<sup>6</sup>  
\$6.2 B for IPF by 2030<sup>7</sup>

# Extensive Clinical Development Pipeline



# Dysfunctional Serotonin or Dopamine Signaling is Implicated in the Pathobiology of Psychiatric Disorders and Inflammatory Diseases

Neuropsychiatric diseases are associated with dysfunctional serotonin and dopamine signaling and dysregulated immune responses

Serotonin signaling is implicated in inflammatory diseases including PAH, IPF and psoriasis

## Neuropsychiatric Disorders

Positive Symptoms	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>			
Negative Symptoms	D <sub>4</sub>	5-HT <sub>1A</sub>	5-HT <sub>2A</sub>	5-HT <sub>7</sub>		
Cognitive Symptoms	D <sub>4</sub>	5-HT <sub>1A</sub>	5-HT <sub>2A</sub>	5-HT <sub>7</sub>		
Depressive Symptoms		5-HT <sub>1A</sub>	D <sub>2</sub>	5-HT <sub>2A</sub>	5-HT <sub>2B</sub>	D <sub>4</sub> 5-HT <sub>7</sub>
ADHD Symptoms	D <sub>4</sub>	5-HT <sub>1A</sub>	5-HT <sub>2B</sub>	5-HT <sub>7</sub>		

## Pulmonary Diseases (PAH and IPF)

Vasoconstriction	5-HT <sub>2A</sub>	5-HT <sub>2B</sub>	
Fibrosis and Inflammation	5-HT <sub>2A</sub>	5-HT <sub>2B</sub>	5-HT <sub>7</sub>
Thrombosis	5-HT <sub>2A</sub>		






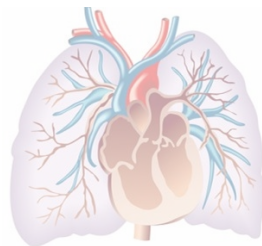
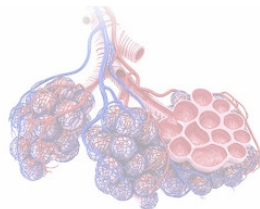
## Psoriasis

Immune Dysfunction	D <sub>2</sub>	D <sub>4</sub>	
Inflammation and Fibrosis	5-HT <sub>2A</sub>	5-HT <sub>2B</sub>	5-HT <sub>7</sub>



# Potential Market Opportunity for Brilaroxazine

Addressing Significant Unmet Medical Needs: Psychiatric Conditions and Immune System Abnormalities

Neuropsychiatric Indications				Inflammatory Indications		
Schizophrenia	Major Depressive Disorder	Bipolar Disorder	ADHD	Psoriasis	Pulmonary Arterial Hypertension (PAH)	Idiopathic Pulmonary Fibrosis (IPF)
						
<b>\$10.1B</b> <i>by 2028<sup>1</sup></i>	<b>\$24.5B</b> <i>by 2030<sup>3</sup></i>	<b>\$6.2B</b> <i>by 2027<sup>2</sup></i>	<b>\$29.3B</b> <i>by 2028<sup>4</sup></i>	<b>\$51.2B</b> <i>by 2030<sup>5</sup></i>	<b>\$11.0B</b> <i>by 2030<sup>6</sup></i>	<b>\$6.2B</b> <i>by 2030<sup>7</sup></i>



A stylized, glowing illustration of a human brain, rendered in vibrant blue and purple hues, set against a dark, textured background. The brain is shown in profile, facing right, and is surrounded by a network of glowing, fiber-like structures that suggest neural activity or connectivity.

## Neuropsychiatric Programs

Schizophrenia | Bipolar Disorder |  
Major Depressive Disorder | ADHD

# Schizophrenia Prevalence and Unmet Needs

No current therapies address all needs of patients

Schizophrenia affects ~1.1% of the world's population and ~3.5 million people in the US<sup>1</sup> and ~24 million globally<sup>2</sup>

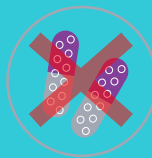
Need for therapies that adequately address the complex mix of positive & negative symptoms, mood, and associated cognitive impairment<sup>3</sup>



## Suboptimal Efficacy<sup>4,5,6,8</sup>

### Not all symptoms addressed

- Negative symptoms
- Cognitive deficits
- Mood symptoms
- Inflammation / Immune System Abnormalities



## Poor Tolerability/ Side Effects<sup>5</sup>

### Poor Tolerability/Side Effects

- Neurological (EPS, akathisia)
- Endocrine (hormones imbalance, sexual dysfunction)
- Metabolic (obesity, diabetes, cholesterol)



## High Discontinuation/ Non-Compliance<sup>6,7</sup>

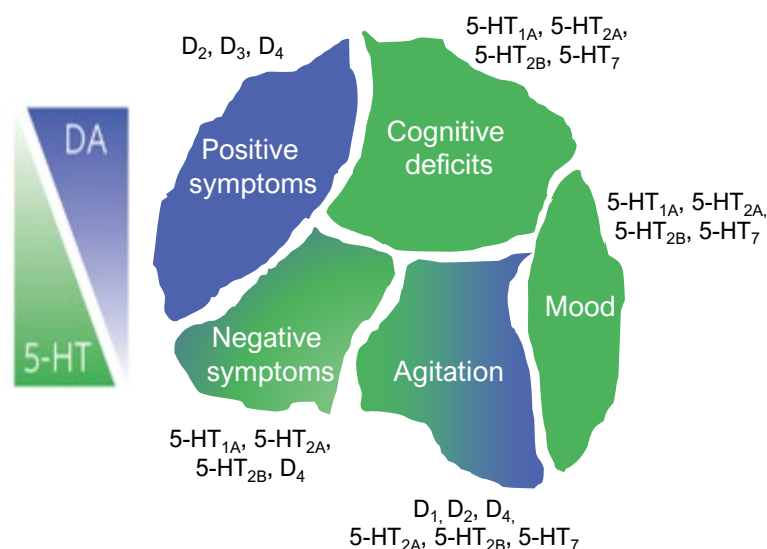
### Estimated discontinuation rates

- 30-50% in short-term treatment of acute patients
- 42-74% in long-term treatment of stable patients

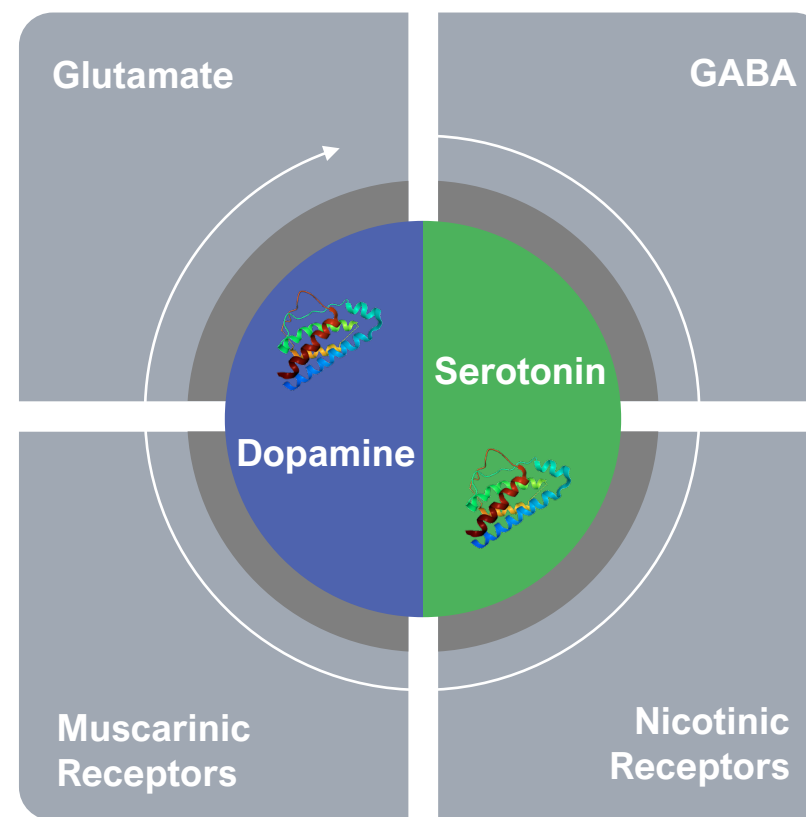


# Many Psychiatric Disorders are Primarily Driven by Dysfunctional Serotonin and Dopamine Signaling

Targeting serotonin and dopamine receptors can treat schizophrenia and comorbid symptoms



DA and 5-HT drive pathobiology and symptom domains in schizophrenia, bipolar disorder, major depressive disorder, and attention/deficit hyperactivity disorder



Glutamate, GABA, muscarinic and nicotinic receptors are downstream targets which are affected by dysfunctional dopamine and serotonin signaling system

# Imbalance of Cytokines in Schizophrenia: Putative Treatment Targets

Cytokines mediate cross-talk between the nervous system and the inflammatory response

## Schizophrenia

IL-1 $\beta$  and IL-6

More severe positive symptoms

IL-1 $\beta$ , IL-4, IL-6, INF- $\gamma$ , TNF- $\alpha$ , and TGF- $\beta$

Exacerbated negative symptoms

IL-1 $\beta$ , and IL-6

Worse cognitive abilities

IL-1 $\beta$ , IL-6 and TNF- $\alpha$

Mood symptoms

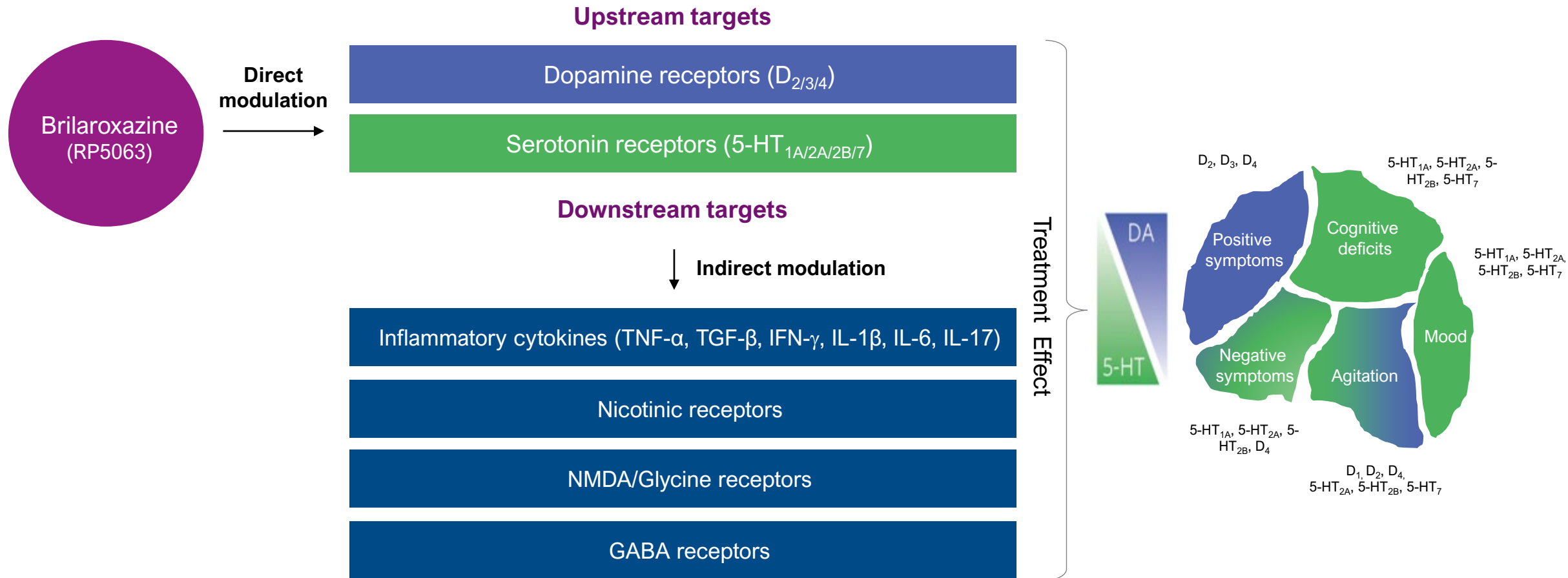
IL-6, IL-17, and TGF- $\beta$

Increased PANSS score

Bhat L, et al. Medical Research Archives 2023, 11(4):3834 ; Reale M et al. Frontiers in Psychiatry 2021, 12:536257; Monji A et al. Japanese Society of Psychiatry and Neurology 2009, 63:257-265.

# Brilaroxazine: Target Engagement and Multifaceted Mechanism of Action

Targeting serotonin and dopamine receptors can treat schizophrenia and comorbid symptoms

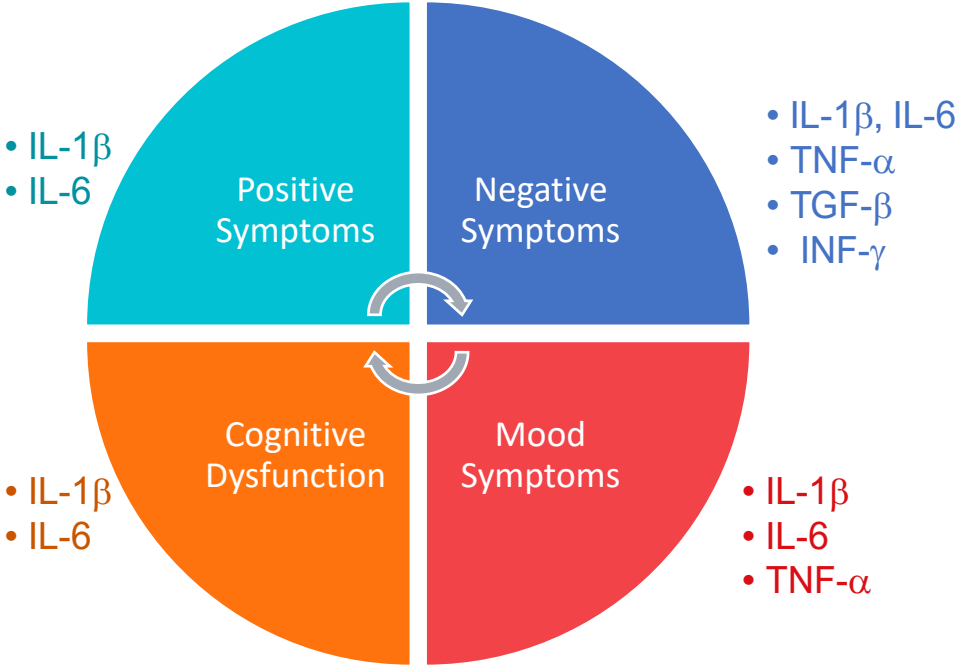


# Brilaroxazine Has a Differentiated Target Receptor Activity Profile

Brilaroxazine Receptor Binding Affinities for Schizophrenia Symptoms <sup>1</sup>		
High (K <sub>i</sub> , nM)*	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
	Serotonin 5-HT <sub>2A</sub>	2.5
	Serotonin 5-HT <sub>2B</sub>	0.19
	Serotonin 5-HT <sub>7</sub>	2.7
Moderate (K <sub>i</sub> , nM)	Nicotine α <sub>4</sub> β <sub>2</sub>	36.3
	Serotonin 5-HT <sub>6</sub>	51
Weak or no significant activity	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, and GI side effects	

\*partial agonists for D<sub>2,3,4</sub> and 5-HT<sub>1A</sub> receptors

**Brilaroxazine** reduced proinflammatory cytokines and chemokines implicated in major symptom domains of schizophrenia in animal models<sup>1,2</sup>



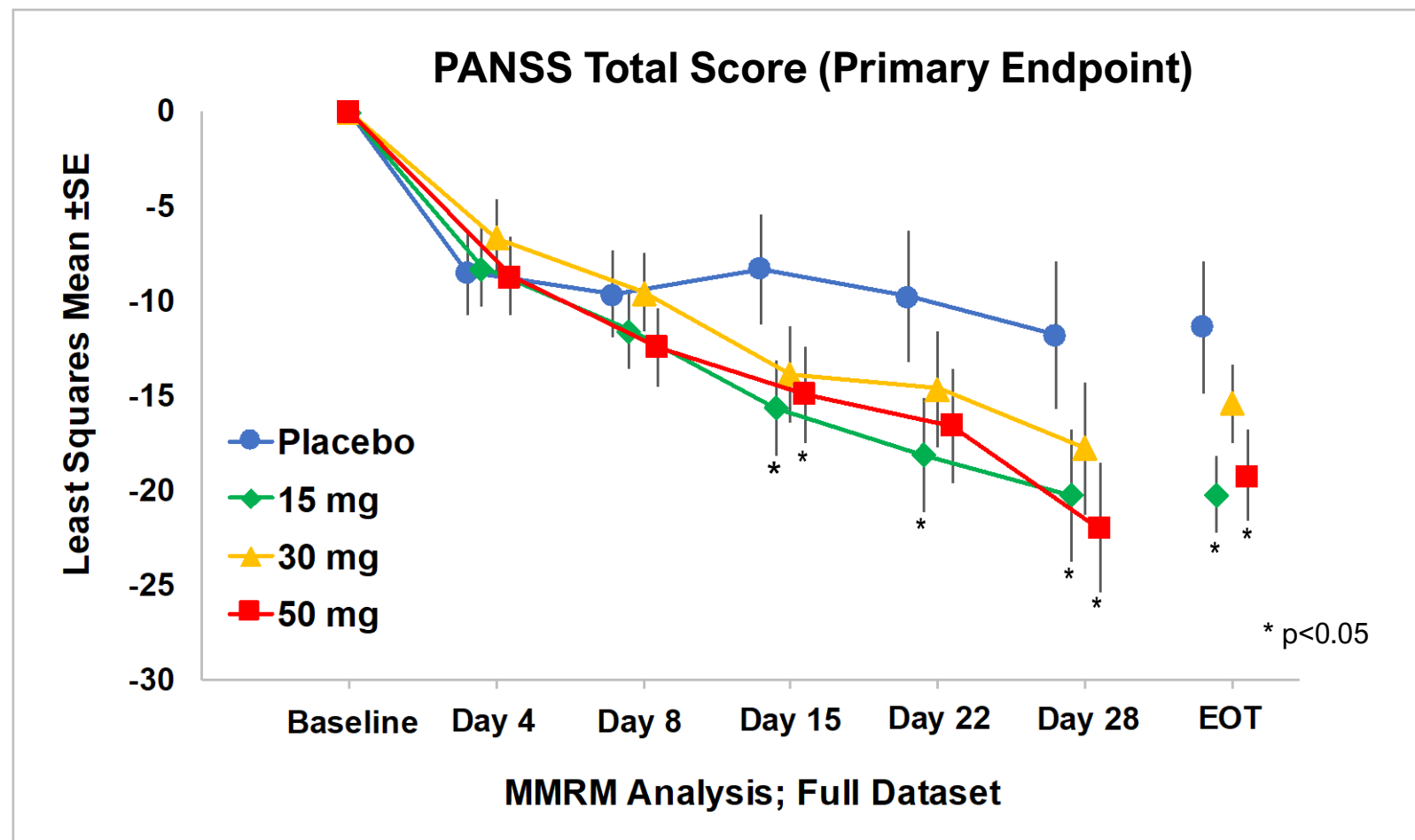


# Schizophrenia Phase 2 Study: Significant Treatment Difference from Placebo

Brilaroxazine demonstrated improved PANSS total score across all dose levels (N=234)

## Efficacy Data for Schizophrenia

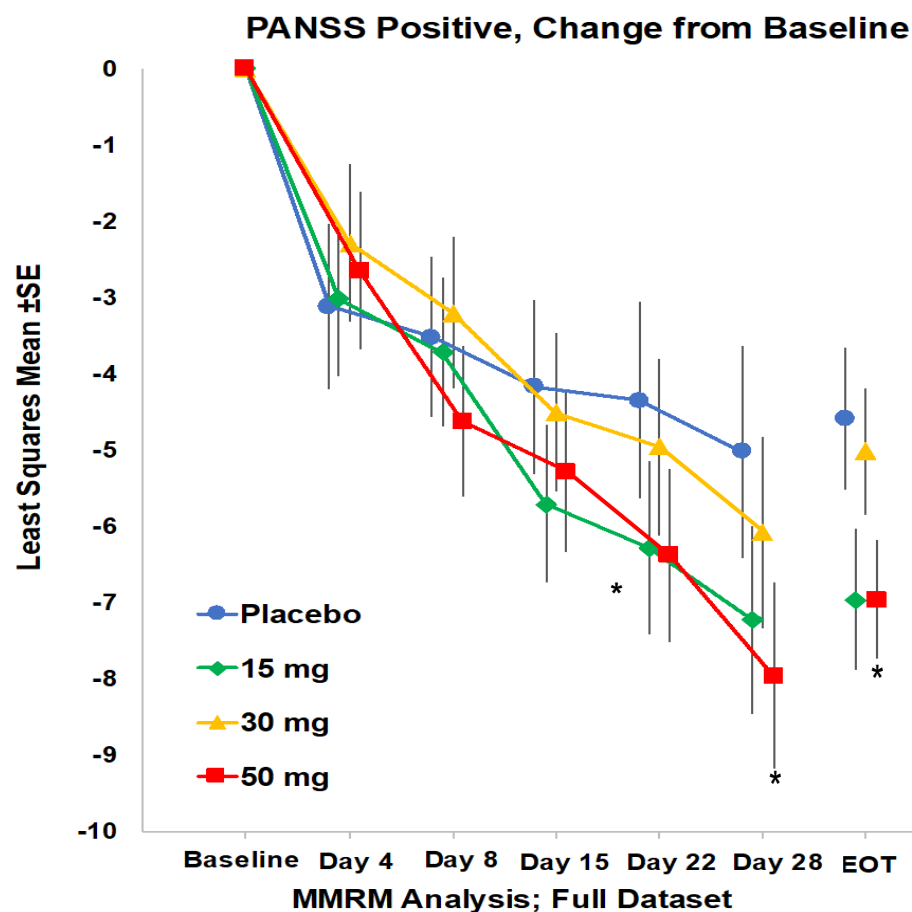
- Study met the safety and efficacy endpoints
- Statistically significant, sustained treatment effect with decrease in PANSS scores
- Treatment effects started separating from placebo within a week



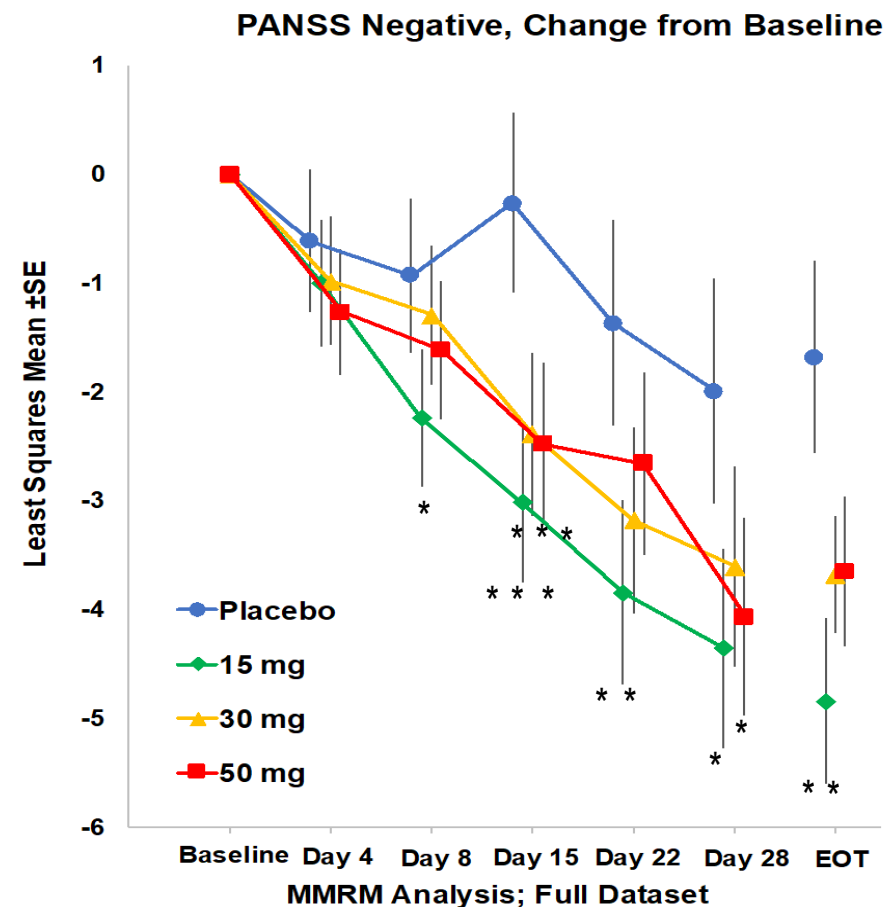
# Brilaroxazine Mitigated Positive and Negative Symptoms

## Phase 2 Study in Schizophrenia

### Decrease in Positive Symptoms



### Decrease in Negative Symptoms

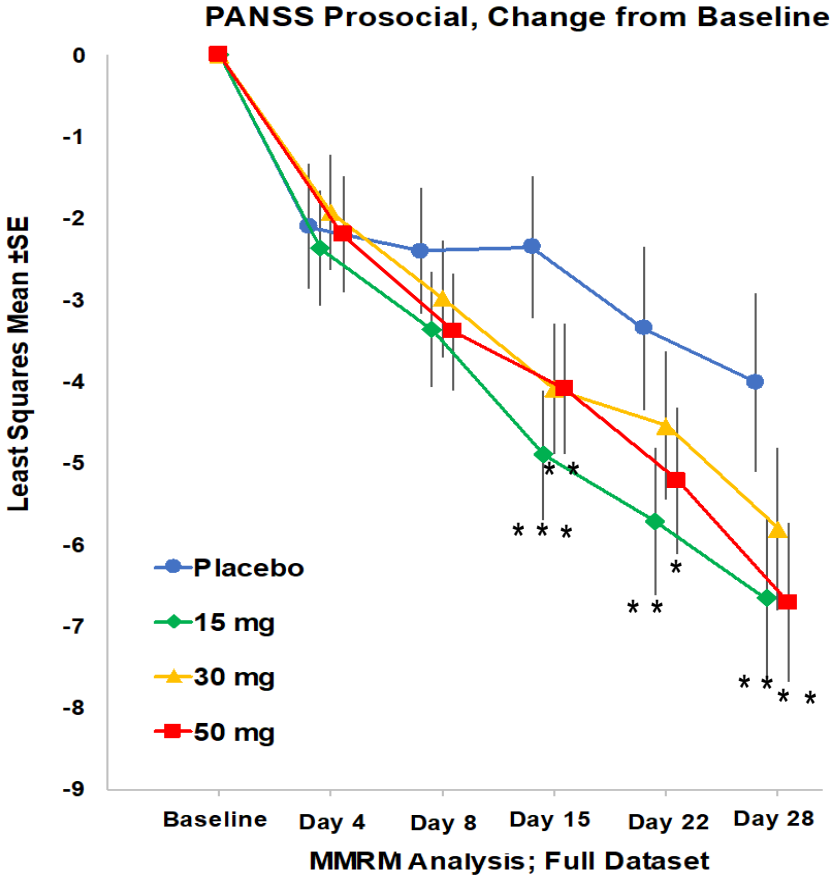


\* p<0.05, \*\* p<0.01, \*\*\* p<0.001

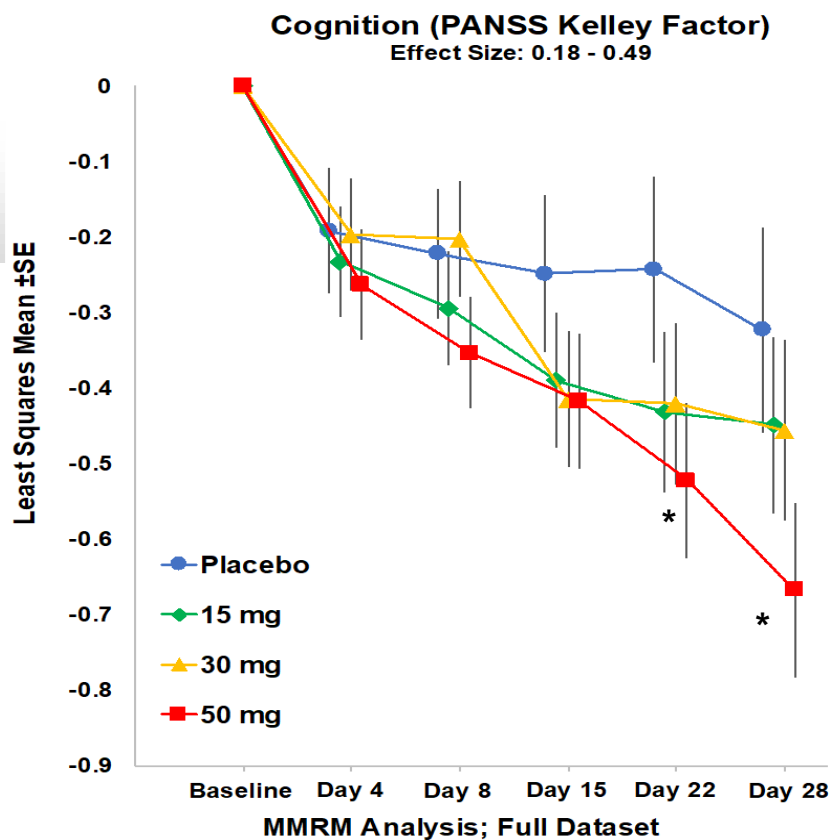
# Brilaroxazine Improved Social Functioning and Cognition

## Phase 2 Study in Schizophrenia

### Improvement in Social Functioning



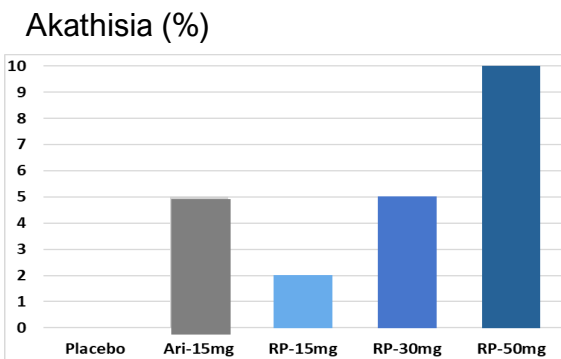
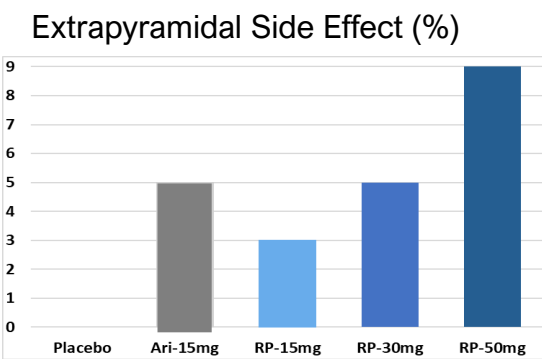
### Improvement in Cognition



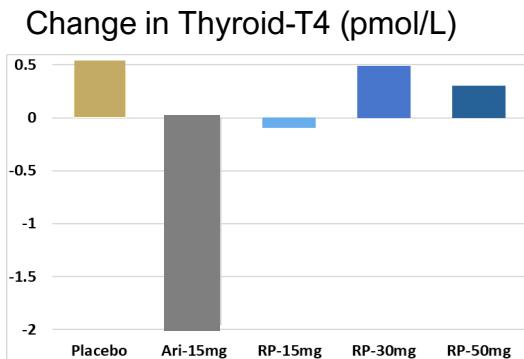
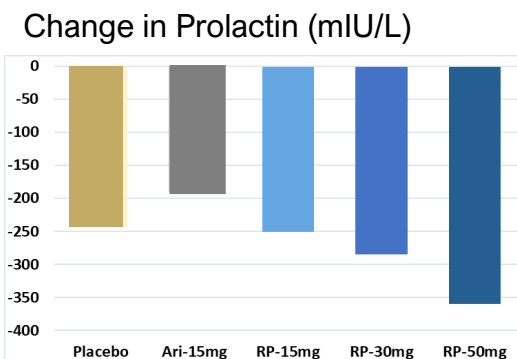
# Schizophrenia Phase 2 Study: Brilaroxazine Side Effect Profile

Neuroleptic, Endocrine and Metabolic Side Effects of Brilaroxazine Comparable to Placebo (N=234)

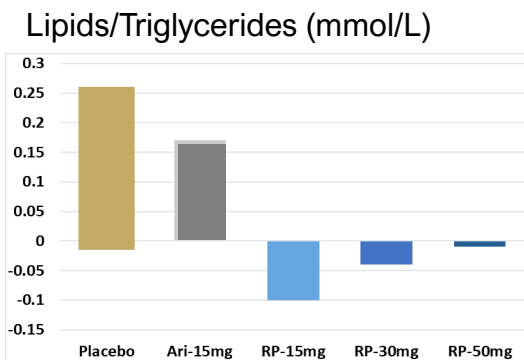
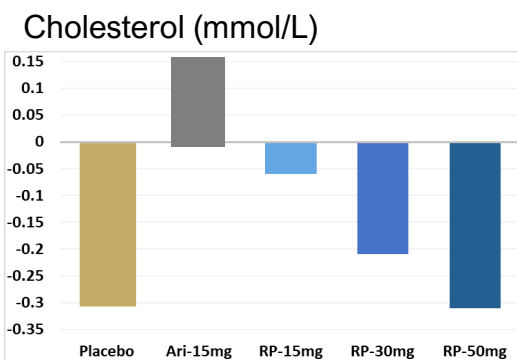
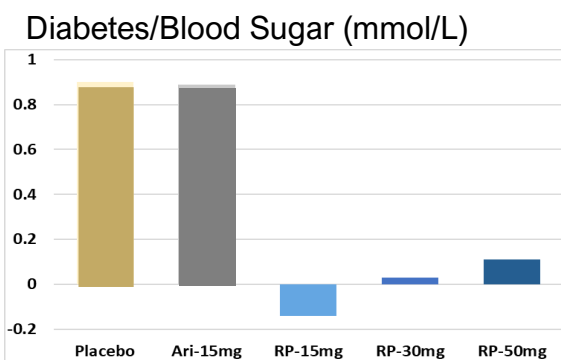
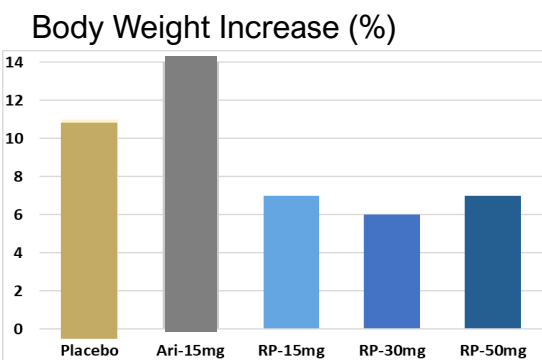
## CNS / Neuroleptic Side Effects



## Endocrine Side Effects



## Metabolic Side Effects



RP: 15mg projected, widely used dose

Ari: Aripiprazole; RP: Brilaroxazine (RP5063)



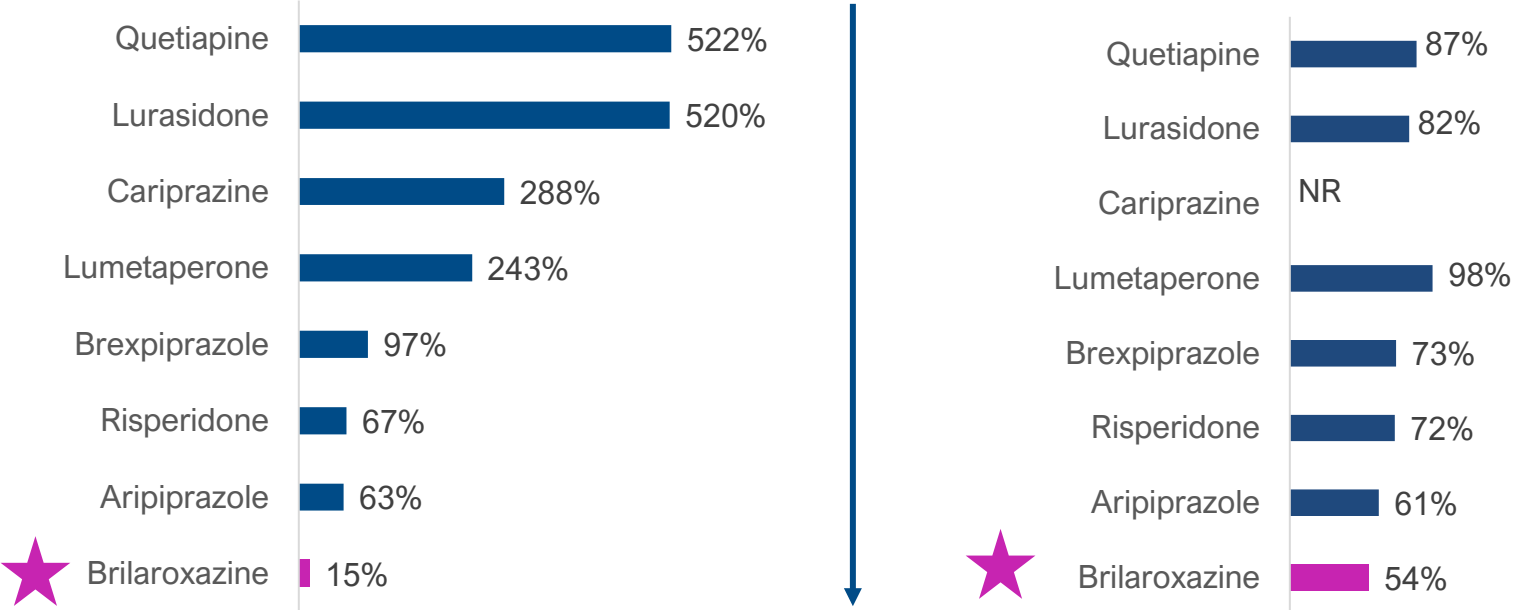
# Lower Clinical Drug-Drug Interactions (DDIs) with Brilaroxazine vs Standards of Care

Up to 34x higher drug plasma concentration with standard of care antipsychotics over brilaroxazine in presence of a strong CYP3A4 inhibitor: A Clinical Differentiation Factor

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**

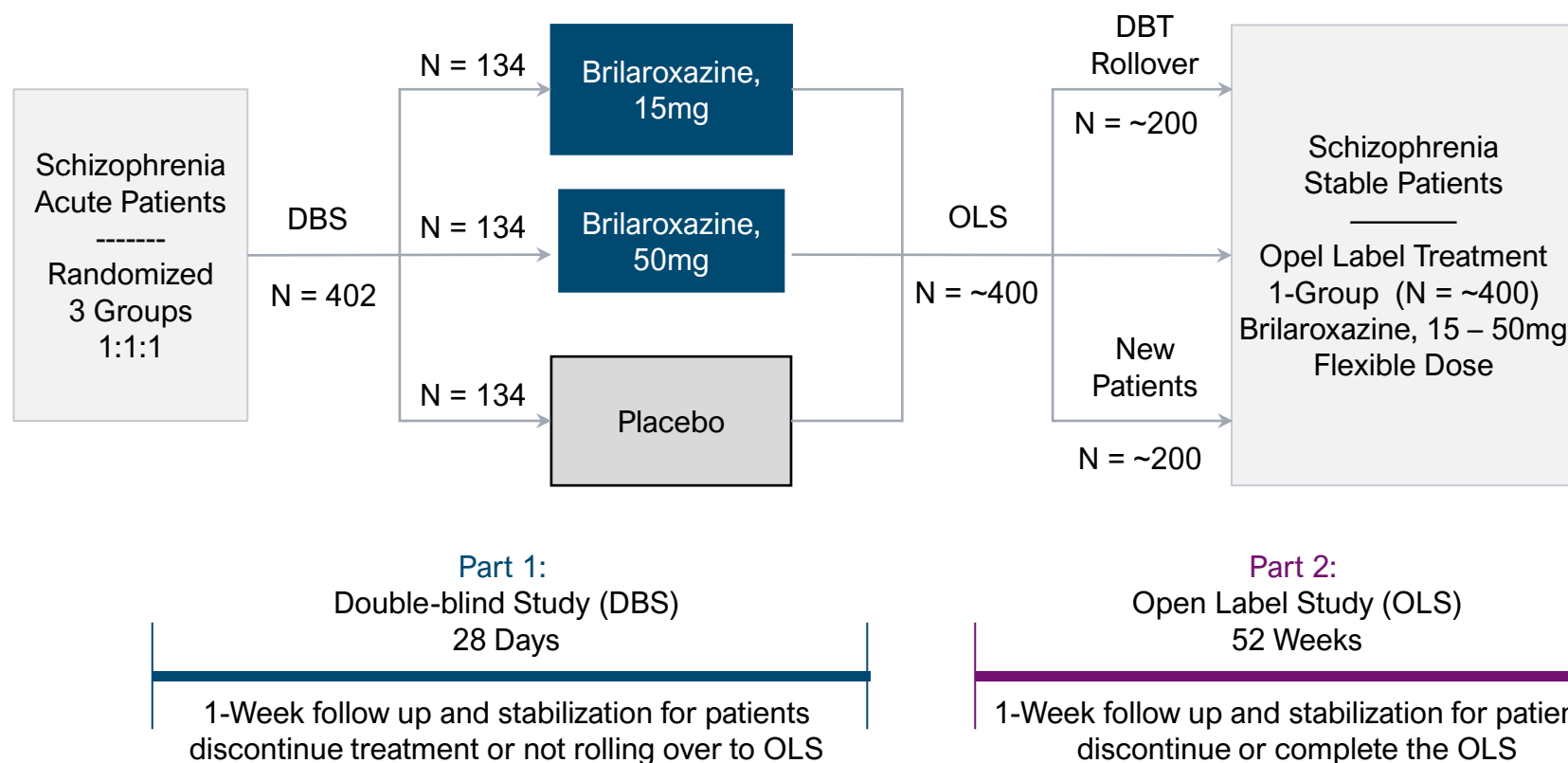


\*Olanzapine<sup>9</sup> not evaluated; metabolized by CYP1A2<sup>10</sup>

(Lower is better)

# Brilaroxazine Phase 3 RECOVER Trial For Schizophrenia (ongoing)

Phase 3, Randomized, 28 Days, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Brilaroxazine in Subjects with an Acute Exacerbation of Schizophrenia, Followed by a 52-Week Open-label Extension



## Study Overview

### Primary Endpoint (DBS):

Reduction in total PANSS at the end of treatment in a brilaroxazine arm from baseline versus placebo

### Safety (DBS, OLS):

Clinical, labs, body weight, lipids, fasting glucose, prolactin

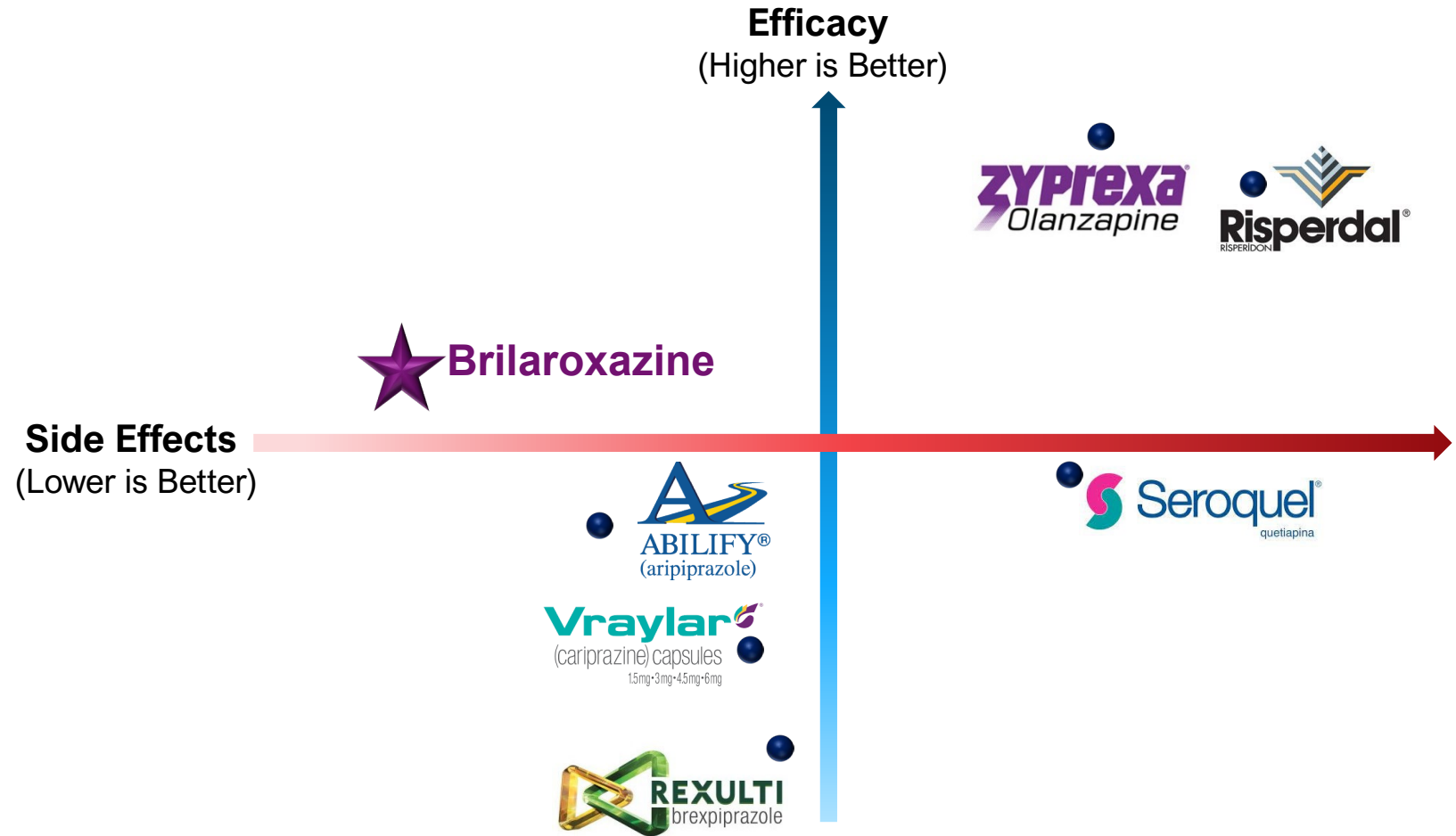
### Pharmacokinetics:

Population pharmacokinetics

# Current Positioning of Brilaroxazine (RP5063) vs. Major Antipsychotics

## Meta-Analysis of Clinical Data of Antipsychotics

Current data suggests that brilaroxazine may have a favorable efficacy and side effect profile vs. currently approved antipsychotics



A doctor in a white lab coat with a stethoscope around their neck is holding a large X-ray of a human chest. The X-ray shows the ribcage and lung fields. The doctor's face is not visible. A blue diagonal line runs across the image from the top left to the bottom right.

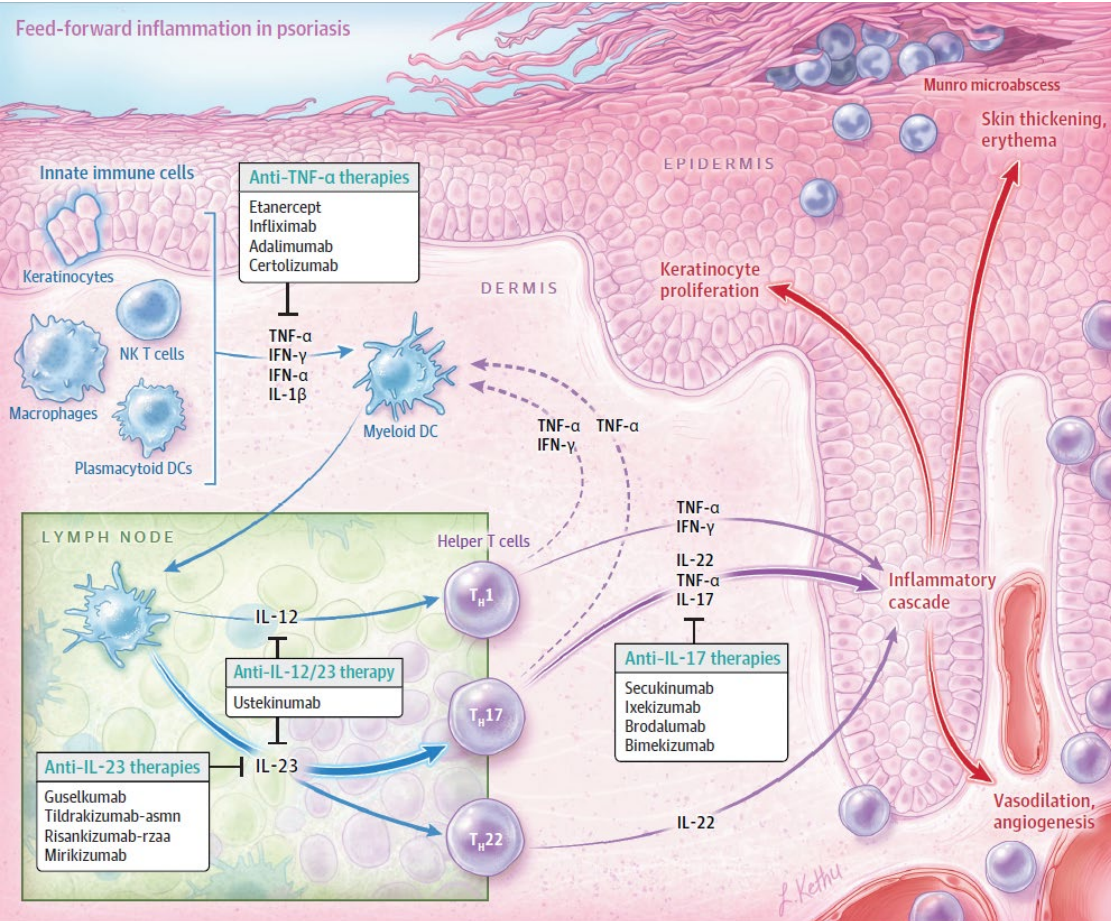
## Inflammatory / Immune Disease Programs

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



# Brilaroxazine has Potential to Treat Psoriasis

Inflammatory skin disease driven by dysfunctional serotonin-dopamine signaling

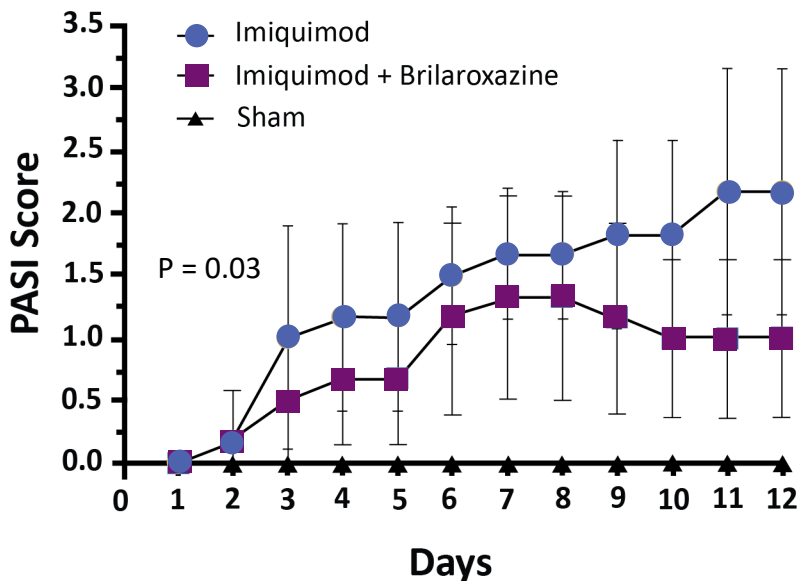


- Approx 3% of the US population and an estimated 125 million people worldwide suffer from psoriasis
- An estimated one-third of neuropsychiatric and neurodegenerative disease patients suffer from psoriasis
- Currently there is no cure for psoriasis
  - Topical corticosteroids therapies remain the cornerstone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

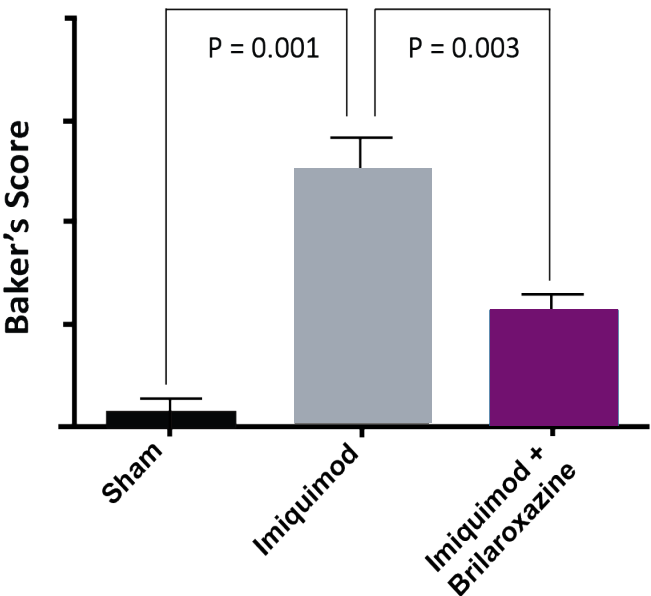
# Brilaroxazine Demonstrated Encouraging Preclinical Efficacy

In an imiquimod induced mouse model of psoriasis

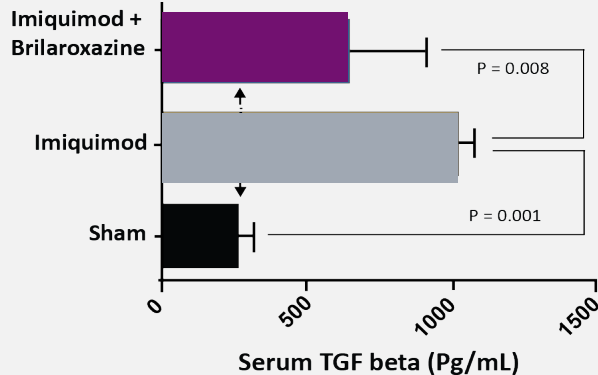
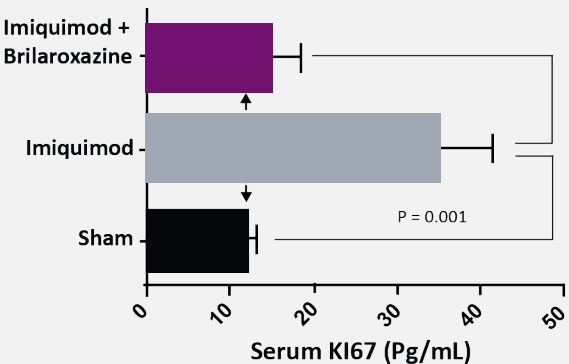
## Psoriasis Area Severity Index (PASI)



## Psoriasis Severity by Baker Score



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



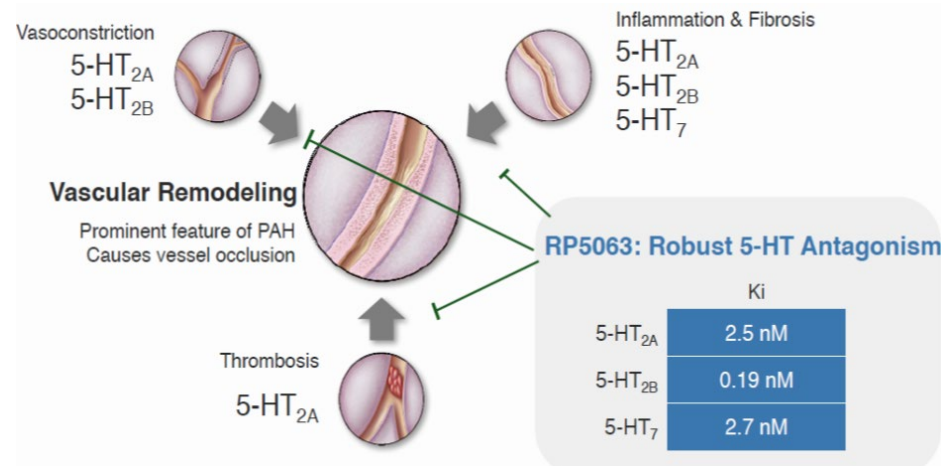
**Brilaroxazine topical liposomal gel significantly decreased**

- 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

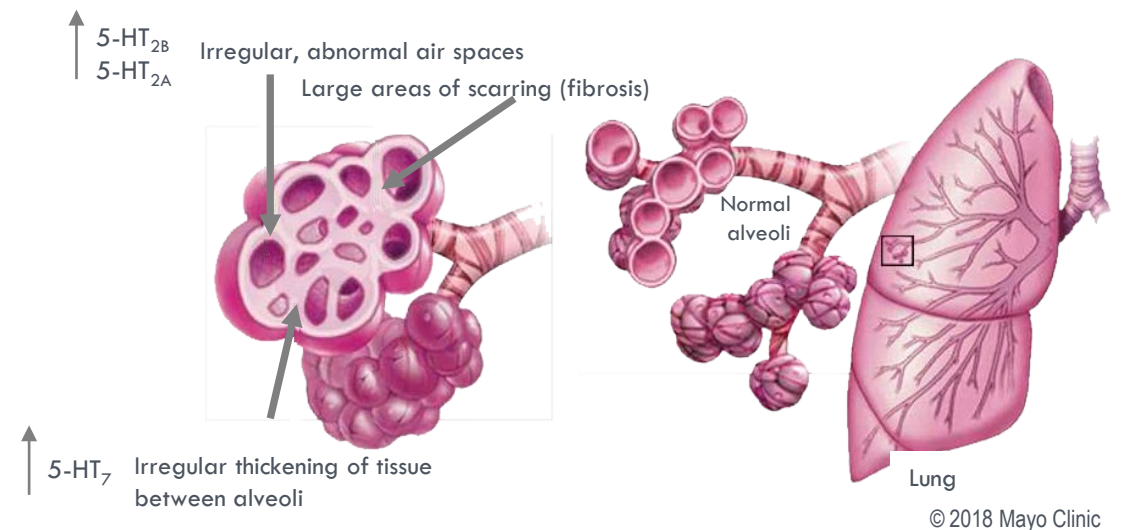
PAH and IPF are Orphan Diseases that involve dysfunctional serotonin signaling

## 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

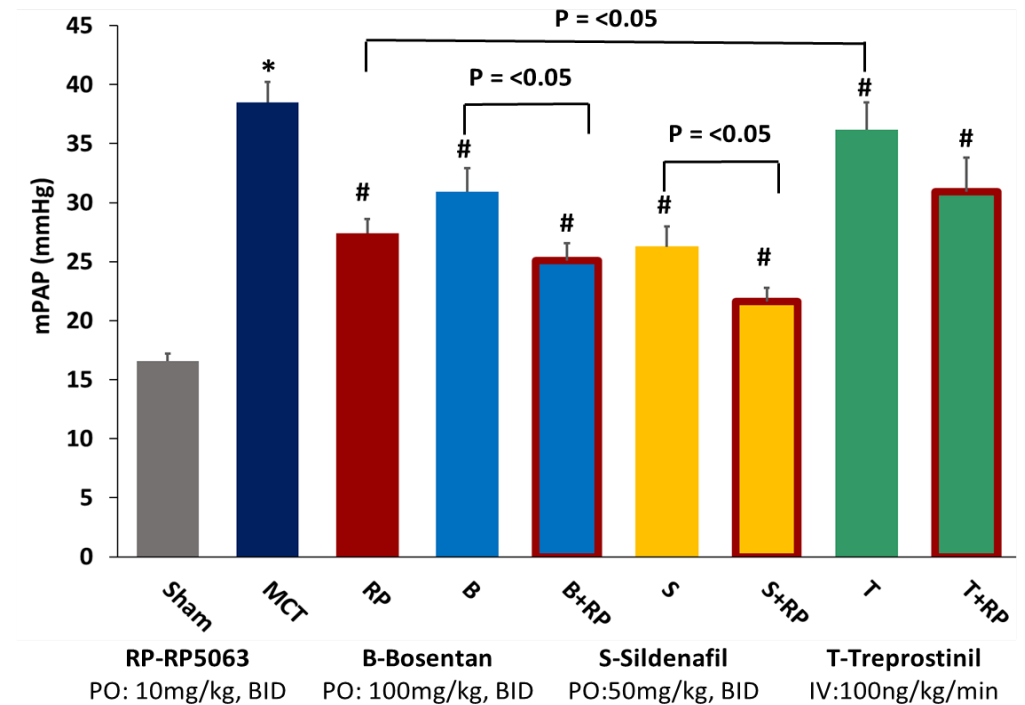
# Brilaroxazine: Encouraging Results in PAH Translational Rodent Models

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

## Brilaroxazine mitigates pulmonary hypertension and lung fibrosis/collagen





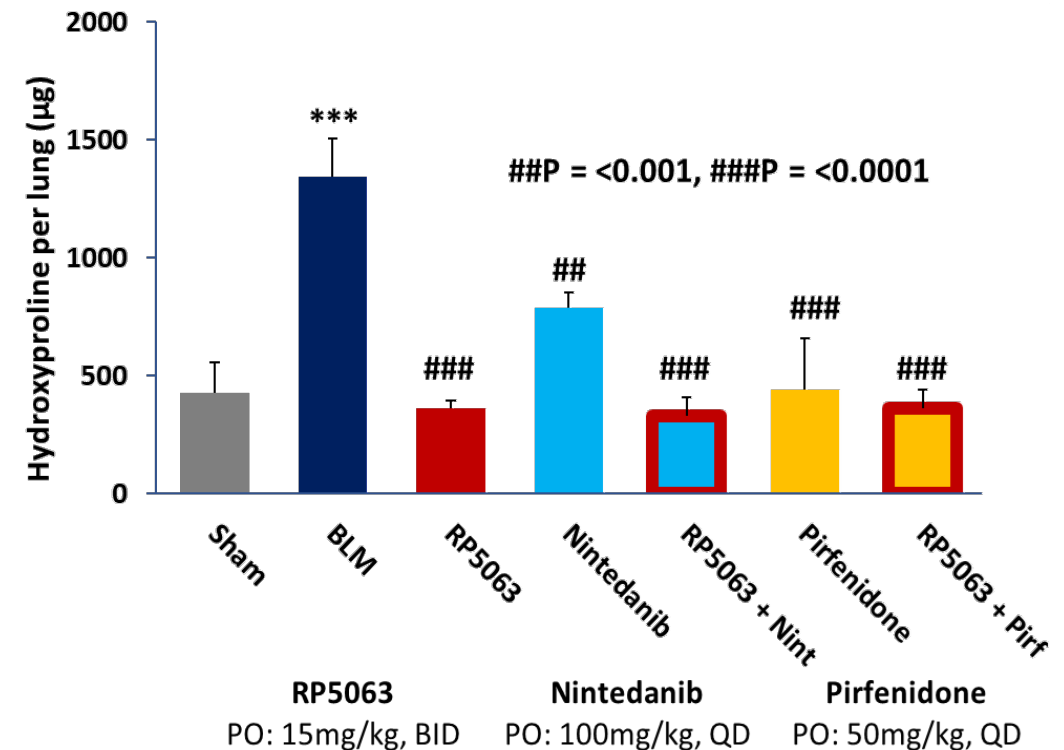
# Brilaroxazine: Encouraging Results in Bleomycin-Induced IPF Rodent Model

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

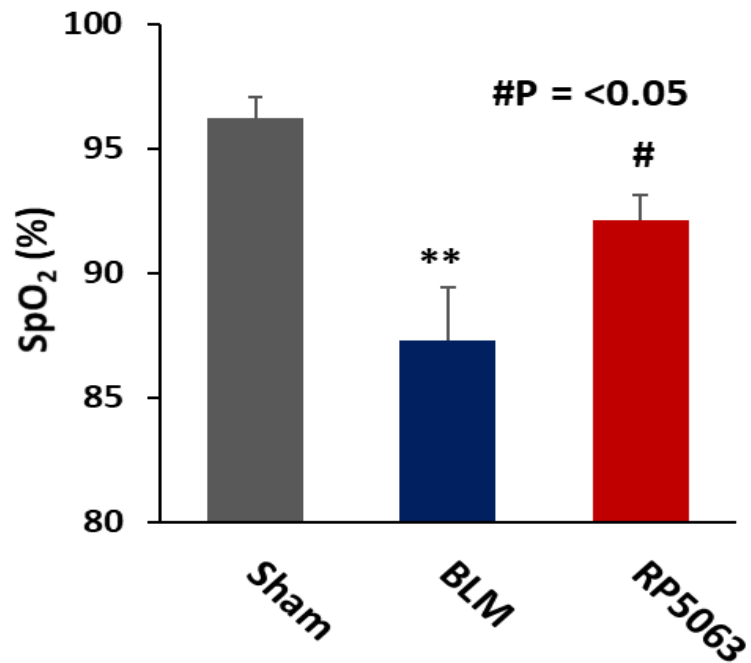
## Brilaroxazine mitigates lung fibrosis / collagen (Decrease in Hydroxyproline)



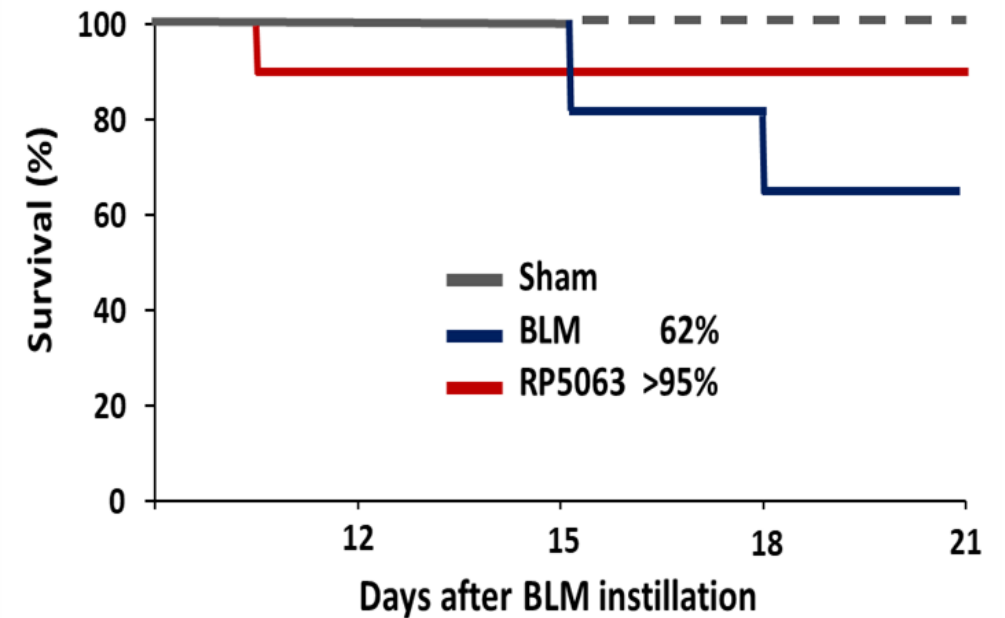
# Brilaroxazine Improves Survival in Bleomycin Induced IPF Rodent Model

Significant Treatment Effect and Functional Outcomes

## Brilaroxazine Mitigates Respiratory Resistance



## Brilaroxazine Improves Survival



# 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

# Experienced Management Team

20+ years of experience in drug discovery and clinical development



**Laxminarayan Bhat, PhD**  
Founder, President and CEO



**Narayan Prabhu, CPA**  
Chief Financial Officer



**Harald Murck, MD**  
Sr VP Clinical Development

**Sangita Ghosh, PhD**  
Sr VP Pharm Development

**Seema Bhat, MS, CTDM, PMP**  
VP Program & Portfolio

**Kevin Charrier**  
VP Quality Assurance



# Pipeline-in-a-Product Opportunities for Lead Asset Brilaroxazine

## Multifaceted Activity for Brilaroxazine

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Differentiated pharmacology profile as modulator of serotonin and dopamine signaling pathways implicated in neuropsychiatric and inflammatory diseases

## Late-Stage Clinical Development

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Ongoing pivotal Phase 3 trial in schizophrenia with expansion potential in neuropsychiatric disorders and inflammatory diseases

## Near-term Catalysts

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Topline data for pivotal Phase 3 trial in schizophrenia expected in Q3 2023



# Reviva Pharmaceuticals Holdings, Inc.

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### International Offices

Bangalore, India

