



REVIVA PHARMACEUTICALS HOLDINGS, INC.

Corporate Presentation, October 2022



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, 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 filings 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



Clinical-stage pharmaceutical company developing new therapies for central nervous system, respiratory, and metabolic 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 mid-2023

Potential for clinical expansion in additional neuropsychiatric disorders and lung diseases

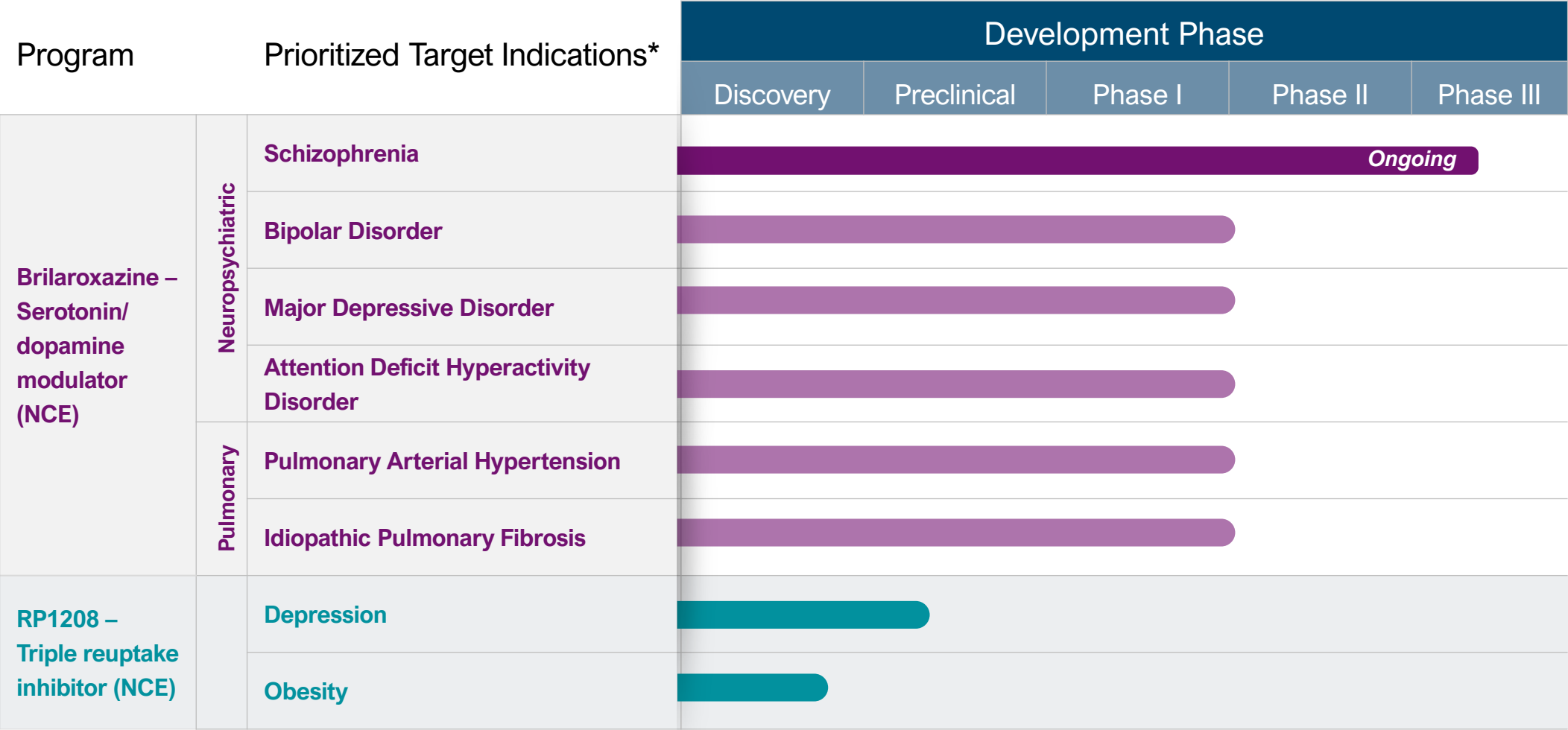
Market Opportunity



Global addressable market size for brilaroxazine:

\$10.1 B for schizophrenia by 2028¹
\$6.2 B for bipolar disorder by 2027²
\$24.5 B for MDD by 2030³
\$29.3 B for ADHD by 2028⁴
\$11.0 B for PAH by 2030⁵
\$6.2 B for IPF by 2030⁶

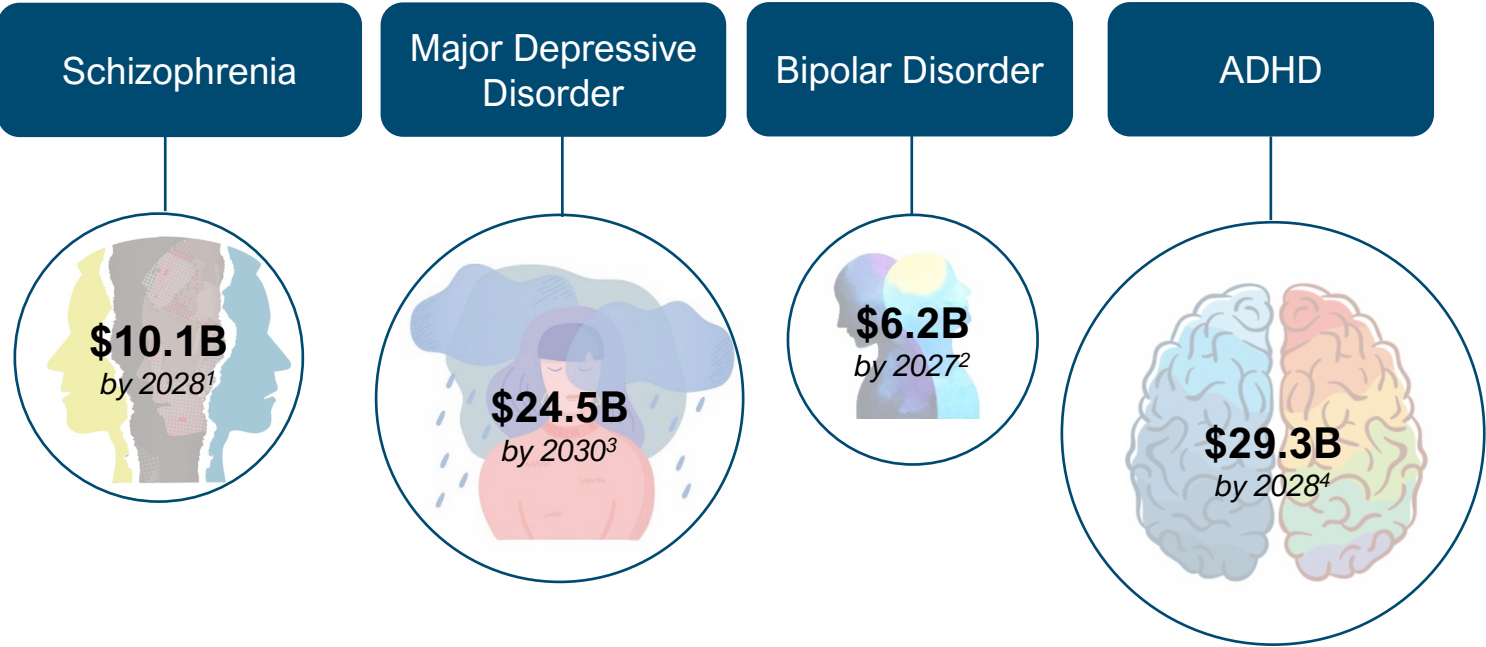
Extensive Clinical Development Pipeline



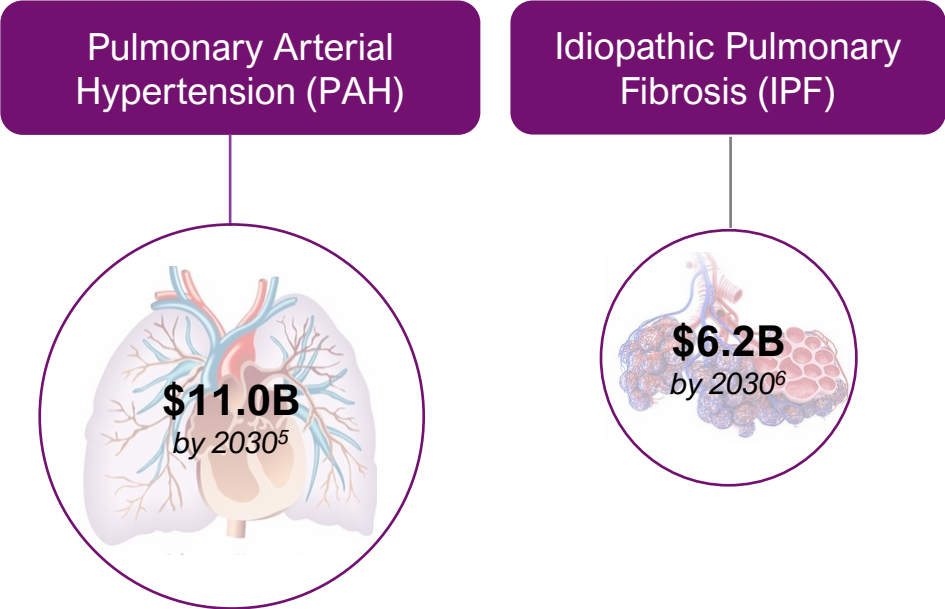
*Opportunity to expand into other indications including Parkinson’s Psychosis and Alzheimer’s (Psychosis/agitation)

Addressing Significant Unmet Medical Needs

Neuropsychiatric Programs



Pulmonary Programs



1.Schizophrenia: Verified Market Research 2021
2.Bipolar Disorder: Maximize Market Research 2021

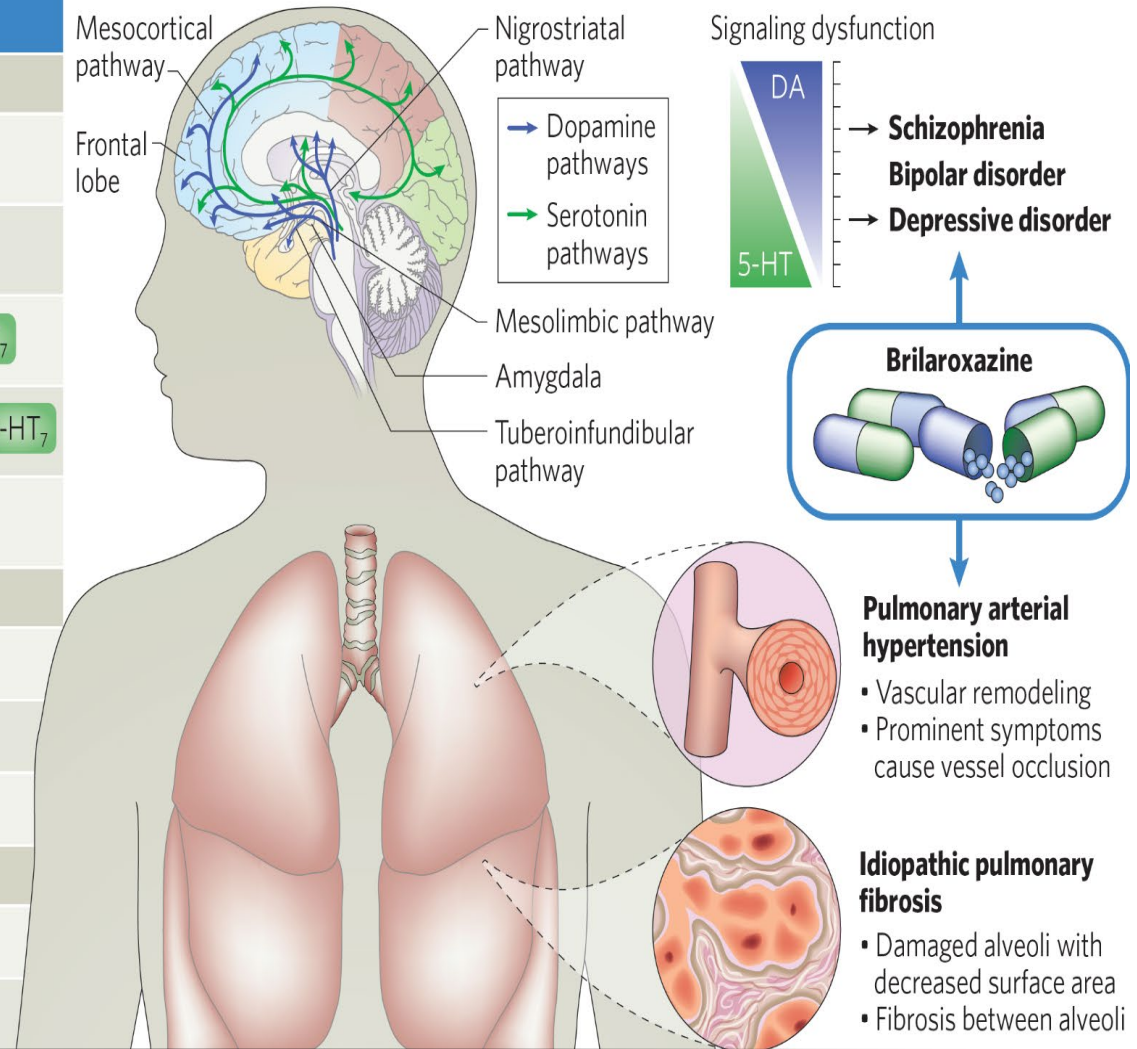
3. MDD: Research and Markets.Com, 2021
4. ADHD: Verified Market Research, 2022

5. PAH: Grand View Research, 2022
6. IPF: Allied Market Research, 2022

Dysfunctional Serotonin Signaling is Implicated in the Pathobiology of Psychiatric Disorders and Lung Diseases

- Brilaroxazine is a potent modulator of serotonin and dopamine signaling pathways
- Dysfunctional serotonin and dopamine signaling pathways are implicated in the pathobiology of neuropsychiatric diseases
- Dysfunctional serotonin signaling is implicated in the pathobiology of lung diseases, PAH and IPF

Dysfunction (region)	Receptors involved
Central nervous system disorders	
Positive symptoms (mesolimbic)	D ₂ D ₃ D ₄
Negative symptoms (mesocortical, PFC)	D ₄ 5-HT _{1A} 5-HT _{2A} 5-HT _{2B}
Cognitive symptoms (dorsolateral PFC)	5-HT _{1A} 5-HT _{2A} 5-HT ₆ 5-HT ₇
Aggressive symptoms (OFC, amygdala)	D ₁ D ₂ D ₄ 5-HT _{2A} 5-HT _{2B} 5-HT ₇
Affective symptoms (ventromedial PFC)	5-HT _{1A} 5-HT _{2B} 5-HT ₇
Pulmonary arterial hypertension	
Vasoconstriction	5-HT _{2A} 5-HT _{2B}
Fibrosis and inflammation	5-HT _{2A} 5-HT _{2B} 5-HT ₇
Thrombosis	5-HT _{2A}
Idiopathic pulmonary fibrosis	
Inflammation	5-HT ₇
Fibrosis	5-HT _{2A} 5-HT _{2B}



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, with intricate, glowing neural pathways and structures visible. The overall effect is one of high-tech, futuristic neuroscience.

Neuropsychiatric Programs

Schizophrenia | Bipolar Disorder |
Major Depressive Disorder | ADHD

Schizophrenia Prevalence and Unmet Needs

No Therapies Adequately Address Symptoms of Schizophrenia

Schizophrenia affects ~1.1% of the world's population and ~3.5 million people in the US¹ and ~24 million globally²

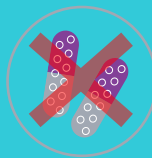
Need for therapies that adequately address the complex mix of positive & negative symptoms, mood, and associated cognitive impairment³



Suboptimal Efficacy^{4,5,6}

Not all symptoms addressed

- Negative symptoms
- Cognitive deficits
- Mood symptoms



Poor Tolerability/ Side Effects⁵

Poor Tolerability/Side Effects

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



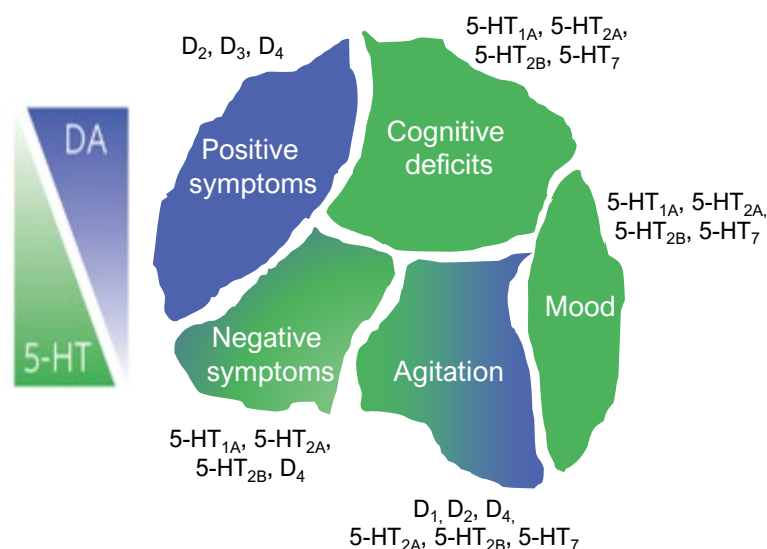
High Discontinuation/ Non-Compliance^{6,7}

Estimated discontinuation rates

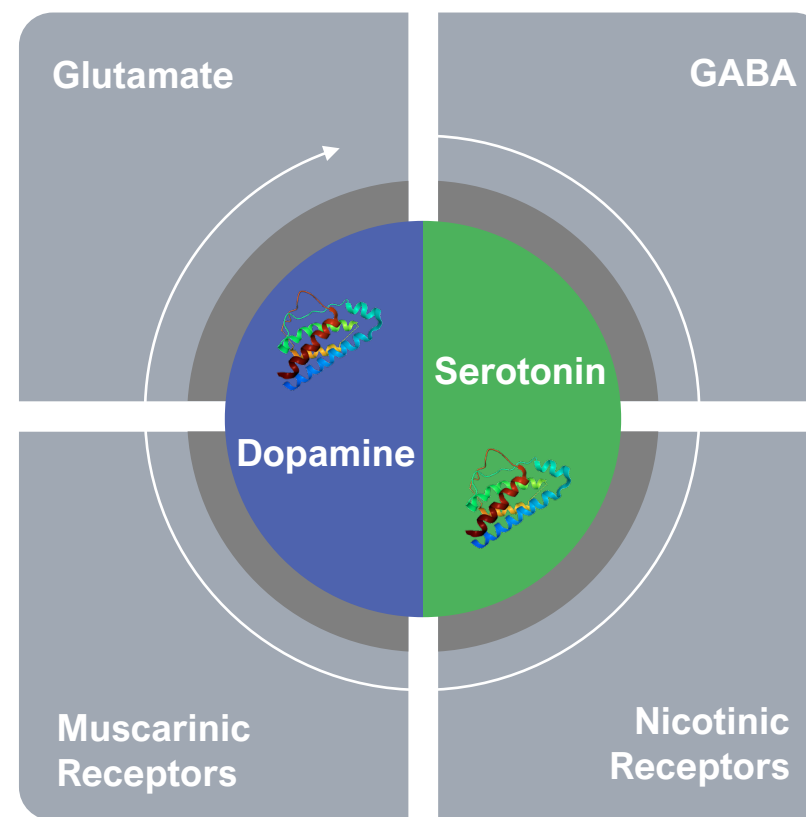
- 30-50% in short-term treatment of acute patients
- 42-74% in long-term treatment of stable patients

Psychiatric Disorders are Primarily Driven by Dysfunctional Serotonin and Dopamine Signaling

Targeting serotonin and dopamine receptors can treat schizophrenia and comorbid symptoms

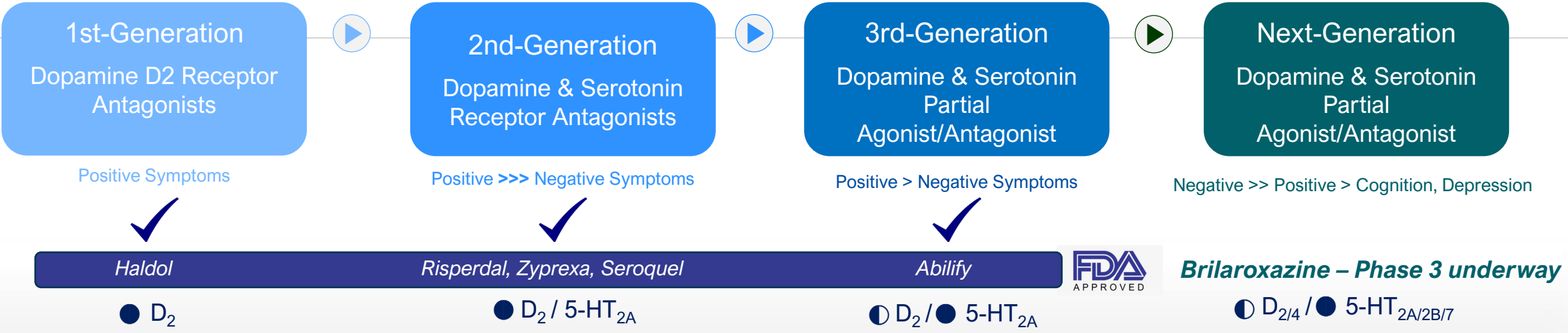


DA and 5-HT drive pathobiology and symptom domains in schizophrenia, bipolar disorder, major depressive disorder, and attention/deficit hyperactivity disorder

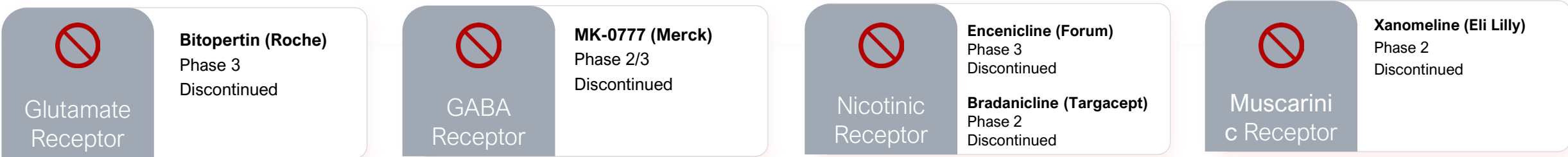


Glutamate, GABA, muscarinic and nicotinic receptors are downstream targets which are affected by dysfunctional dopamine and serotonin signaling system

Serotonin and Dopamine Receptors are Primary Targets for Approved Antipsychotics



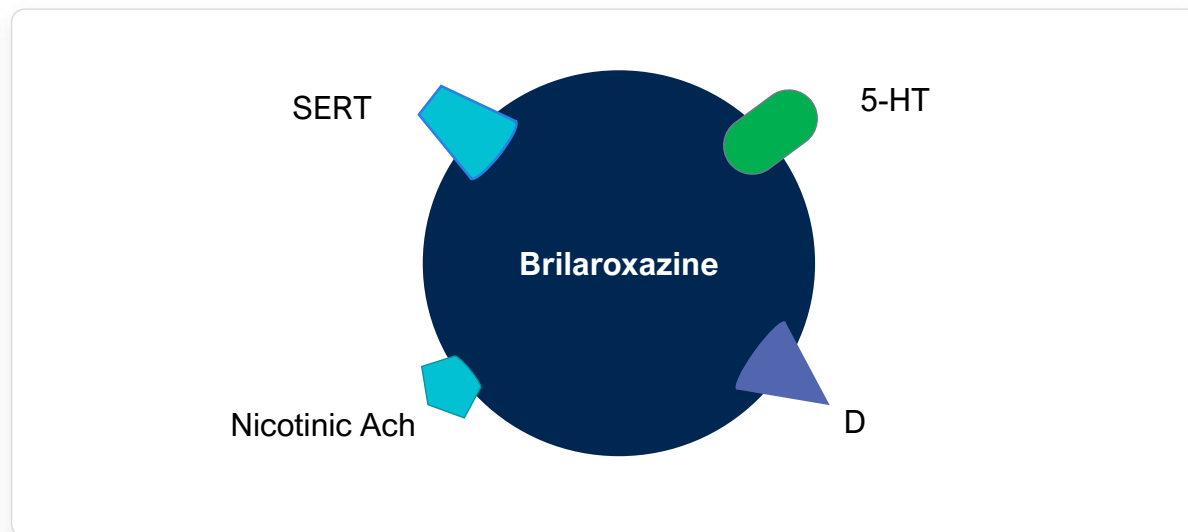
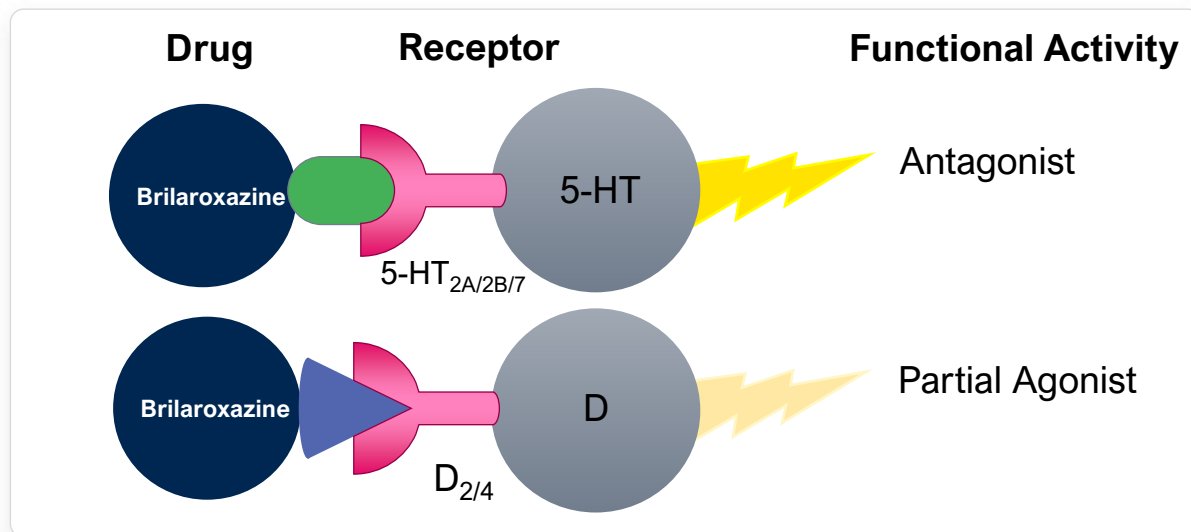
Developmental antipsychotics against downstream targets have failed to demonstrate clinically acceptable efficacy and/or safety



Brilaroxazine: Serotonin and Dopamine Receptor Modulator

Multimodal activity is highly differentiated from other antipsychotics

- **Potent affinity and selectivity** for target receptors implicated in schizophrenia and its comorbid symptoms
- Inhibits key **dopamine (D)** and **serotonin (5-HT)** receptors to stabilize the D/5-HT system
- **High binding affinity** for target receptors D₂, 5-HT_{2A} (Ki: 0.4, 2.5 nM) and 5-HT_{2B}, 5-HT_{1A}, 5-HT₇, D₄ receptors (Ki: 0.19 - 6 nM)
- **Moderate binding affinity** for the serotonin transporter (SERT), 5-HT₆ receptor, and the nicotinic acetylcholine receptor $\alpha_4\beta_2$ (Ki, 30 -100 nM)
- **Weak or no significant activities for off-targets** (5-HT_{2C}, $\alpha_{1,2}$, M₁₋₄) implicated in adverse/side effects

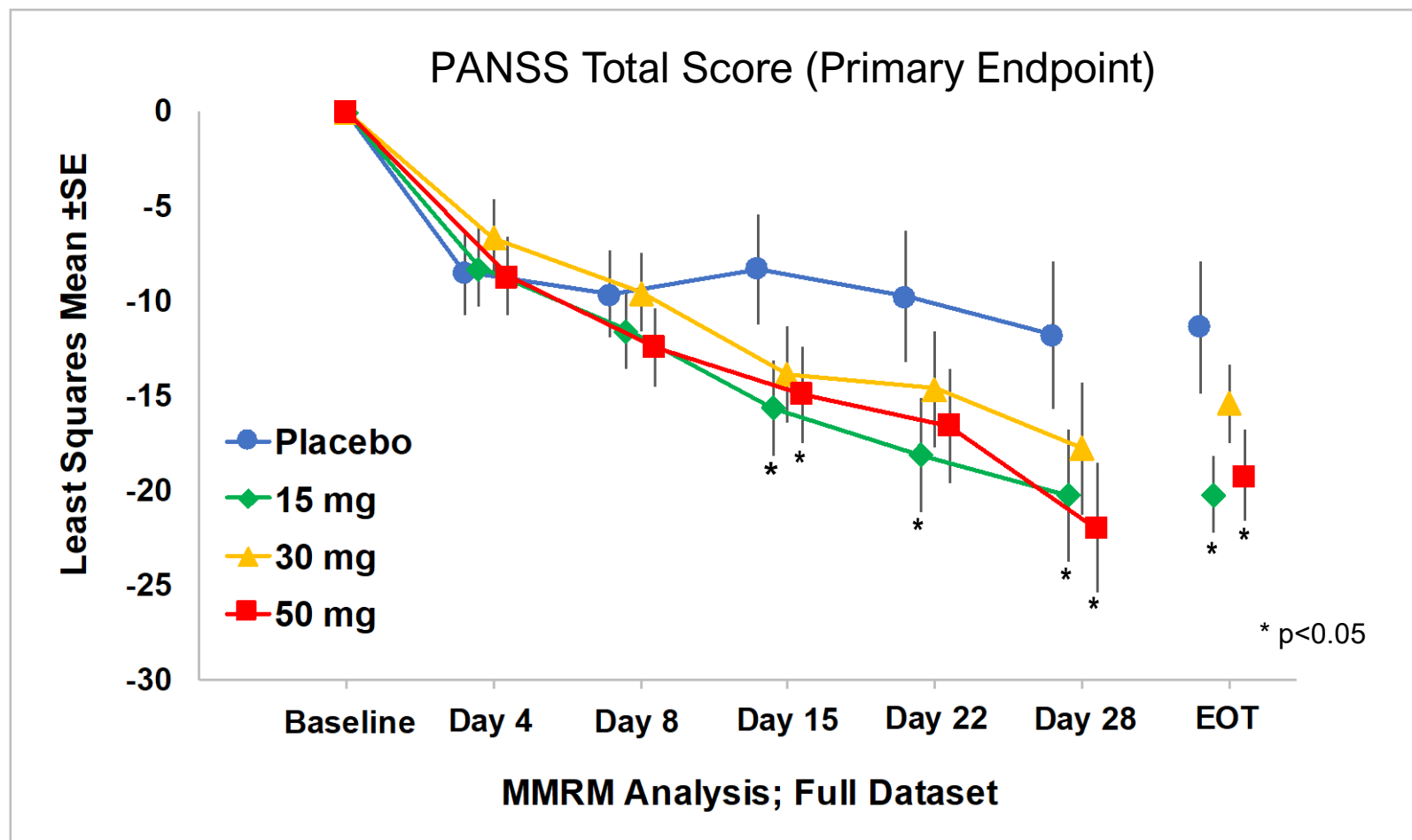


Schizophrenia Phase 2 Study: Significant Treatment Difference from Placebo

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

Efficacy Data for Schizophrenia

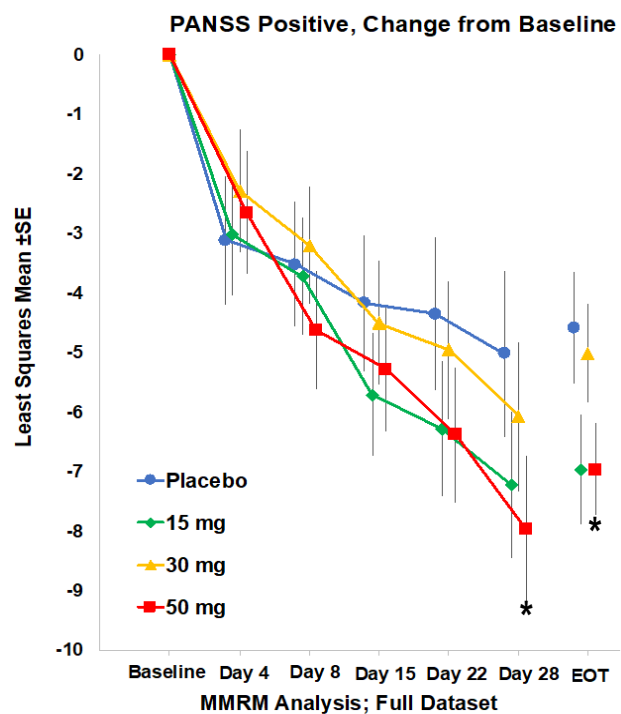
- Study met the safety and efficacy endpoints
- Statistically significant, sustained treatment effect with decrease in PANSS scores
- Treatment effects started separating from placebo within a week



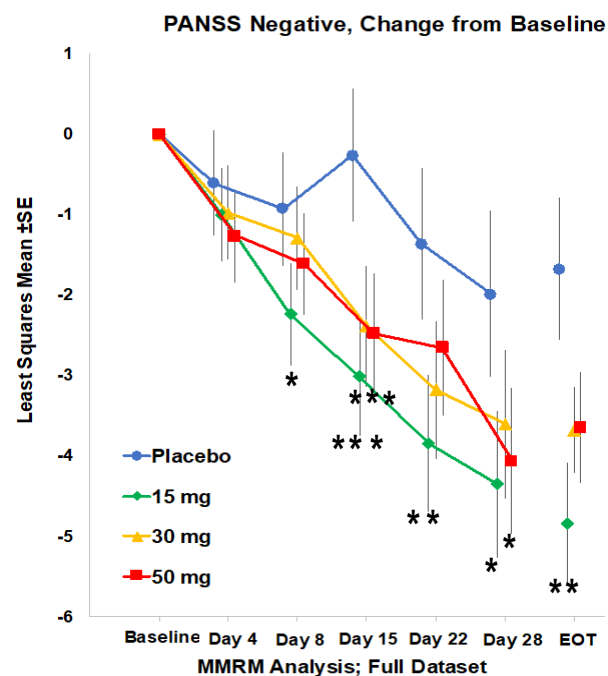
Schizophrenia Phase 2 Study: Significant Treatment Difference from Placebo

Brilaroxazine Mitigated Positive Symptoms, Negative Symptoms, and Improved Prosocial Functioning (N=234)

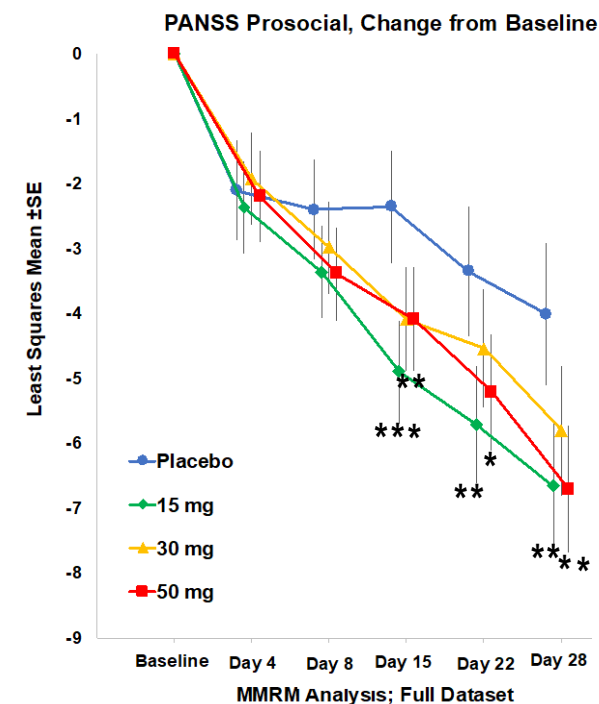
Decrease in Positive Symptoms



Decrease in Negative Symptoms



Improvement in Social Functioning

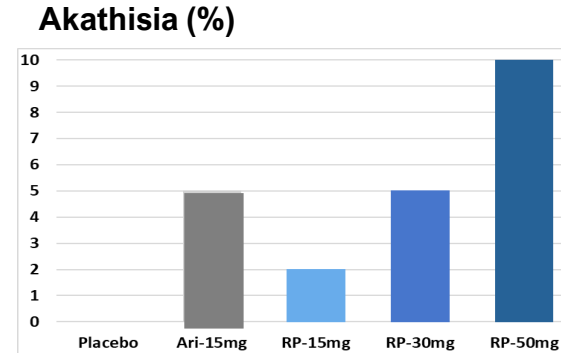
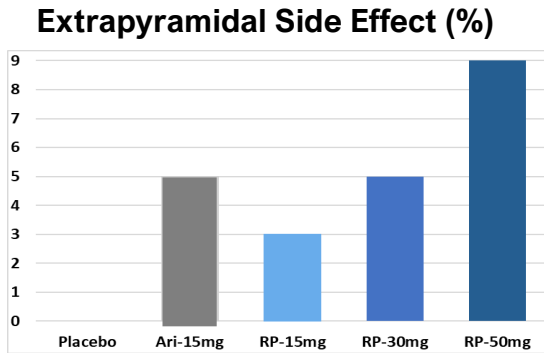


* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

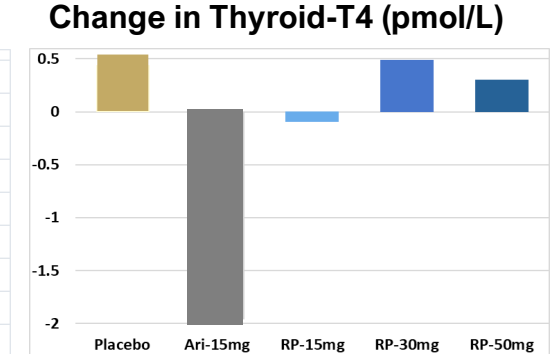
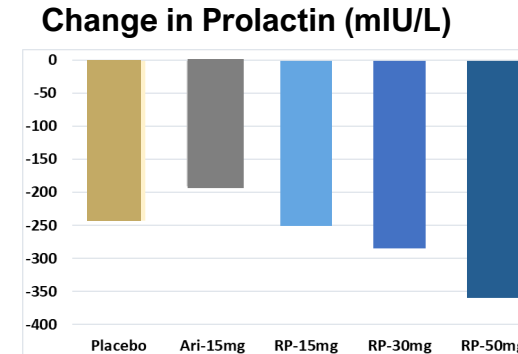
Schizophrenia Phase 2 Study: Brilaroxazine Side Effect Profile

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

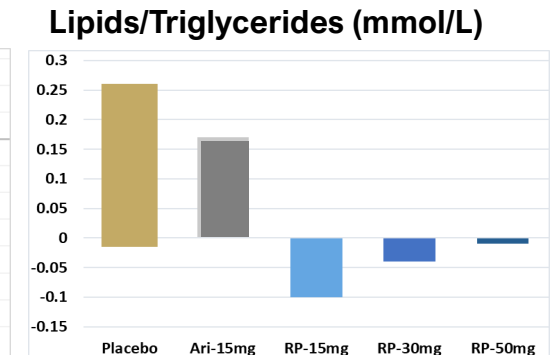
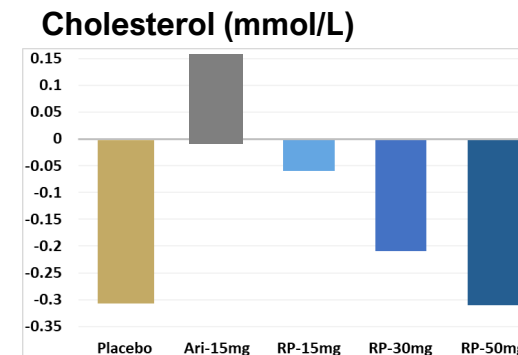
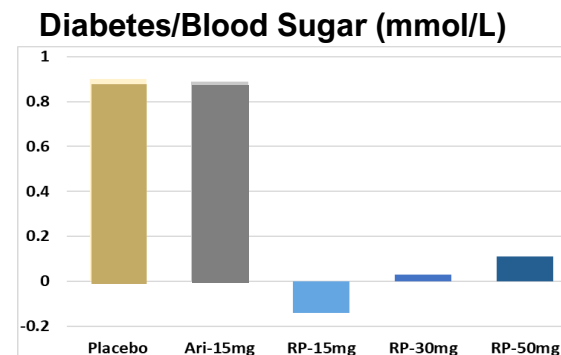
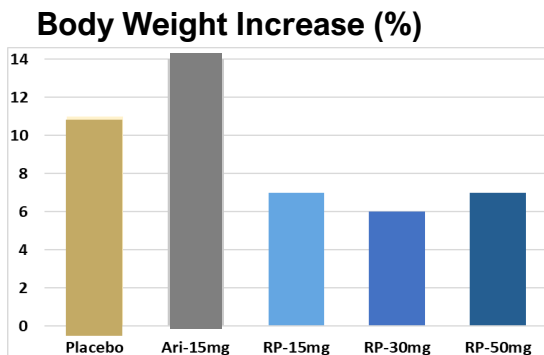
CNS / Neuroleptic Side Effects



Endocrine Side Effects



Metabolic Side Effects



RP: 15mg projected, widely used dose

Ari: Aripiprazole; RP: Brilaroxazine (RP5063)

Brilaroxazine Met Primary & Key Secondary Endpoints in Phase 2 Study

Phase 2 Study Design for Schizophrenia

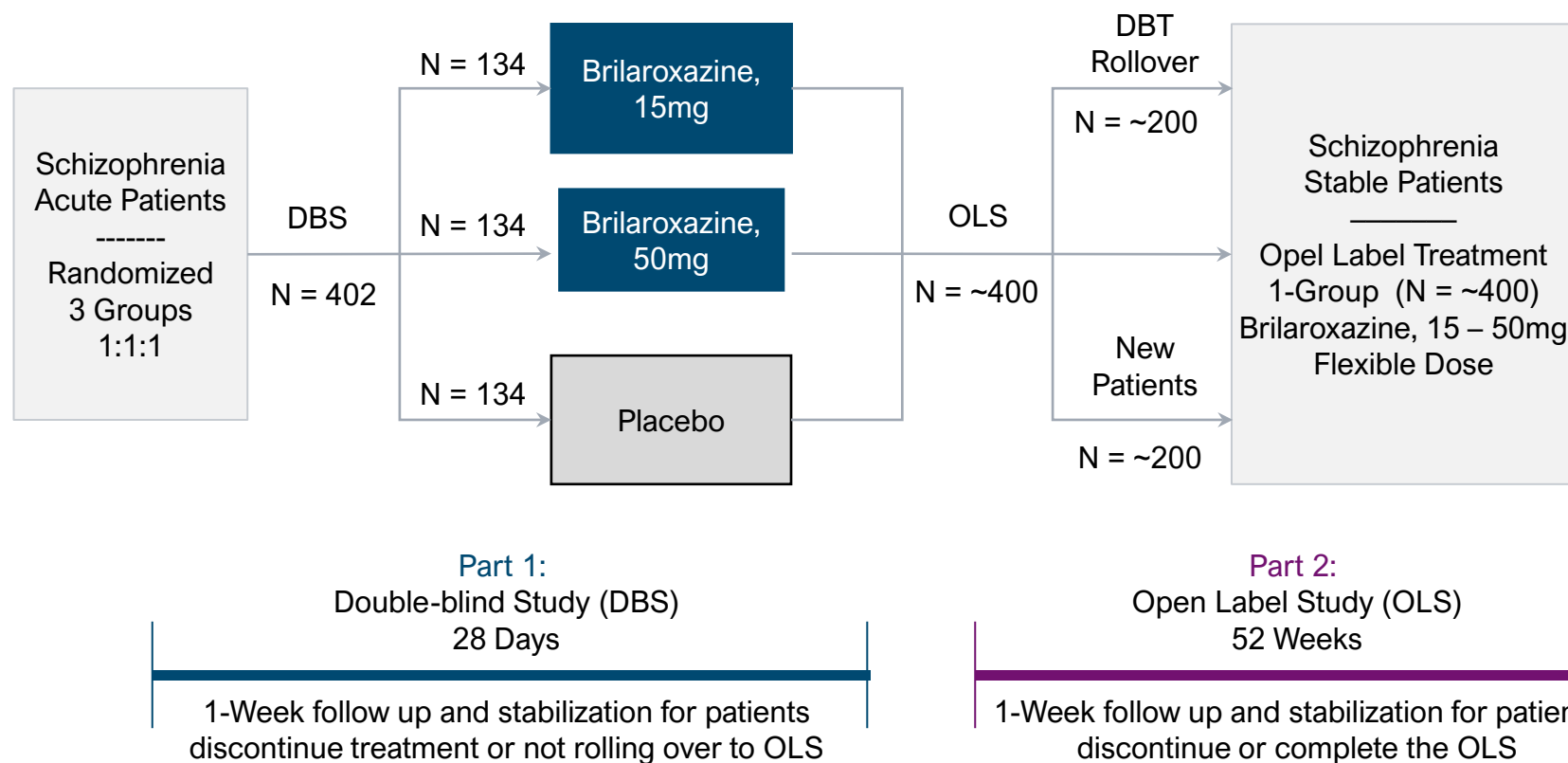
- Patients diagnosed with acute exacerbation of schizophrenia or schizoaffective disorder
- Randomized, double-blind, placebo-controlled, multicenter (US, EU and Asia) trial (N=234, 4-wk)
- 3 Dose levels of brilaroxazine once daily (15, 30, 50 mg)
- Safety and efficacy assessment of brilaroxazine
- Primary endpoints: overall reduction in symptoms, and side effects with brilaroxazine vs placebo
- Secondary endpoints: reduction in symptoms with brilaroxazine vs placebo:
 - Positive Symptoms
 - Negative Symptoms
 - Social Inhibition
 - Depression
 - Cognitive Dysfunction

Key Findings

- Met primary endpoint with statistically significant reduction in schizophrenia on total PANSS scores vs placebo
- Significantly mitigated positive symptoms, negative symptoms and social inhibition with early separation from placebo
- Directional improvement in depression and cognitive symptoms compared to placebo
- Favorable safety profile with no significant change in body weight, blood sugar, lipids, hormones (prolactin, thyroid) and suicidal ideation compared to placebo
- Well tolerated with 0- 2% side effect-related, and 12-14% discontinuation rates for potential marketing doses 15 mg and 50 mg of brilaroxazine

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

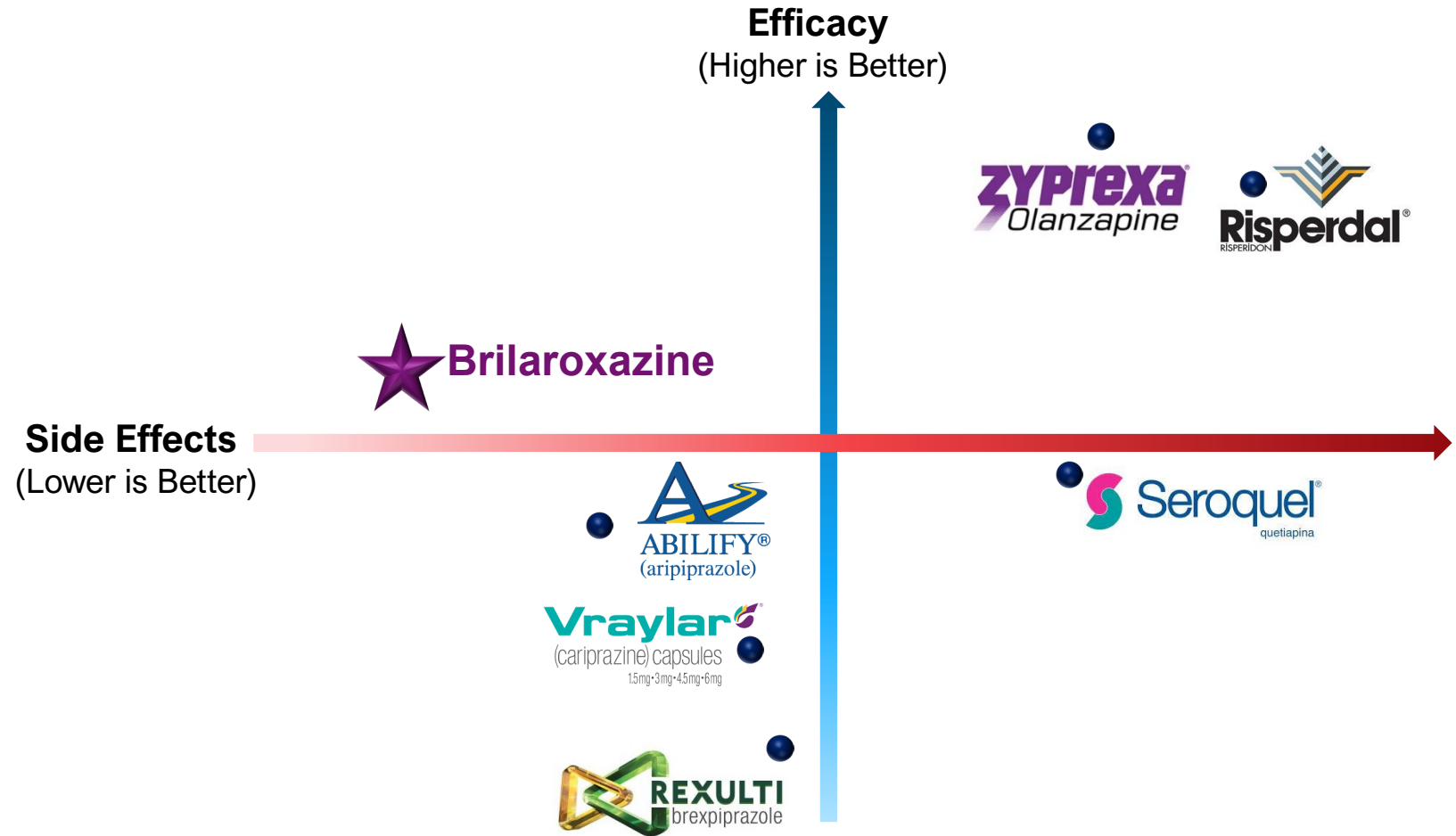
Pharmacokinetics:

Population pharmacokinetics

Current Positioning of Brilaroxazine vs. Major Antipsychotics

Meta-Analysis of Clinical Data of Antipsychotics

Brilaroxazine has 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 rib cage and lung fields. 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.

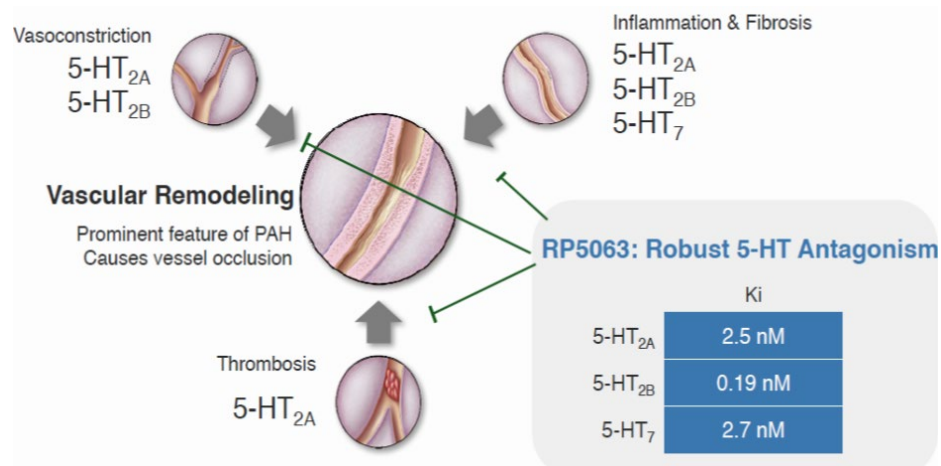
Pulmonary Programs

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

Brilaroxazine: Potential to Delay PAH and IPF Disease Progression

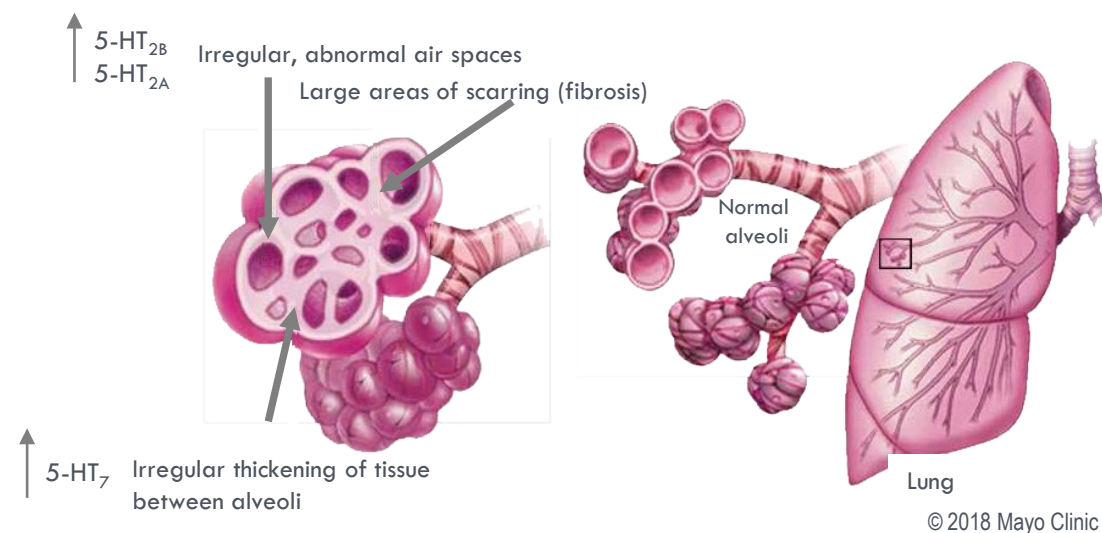
PAH and IPF are Orphan Diseases that involve dysfunctional serotonin signaling

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

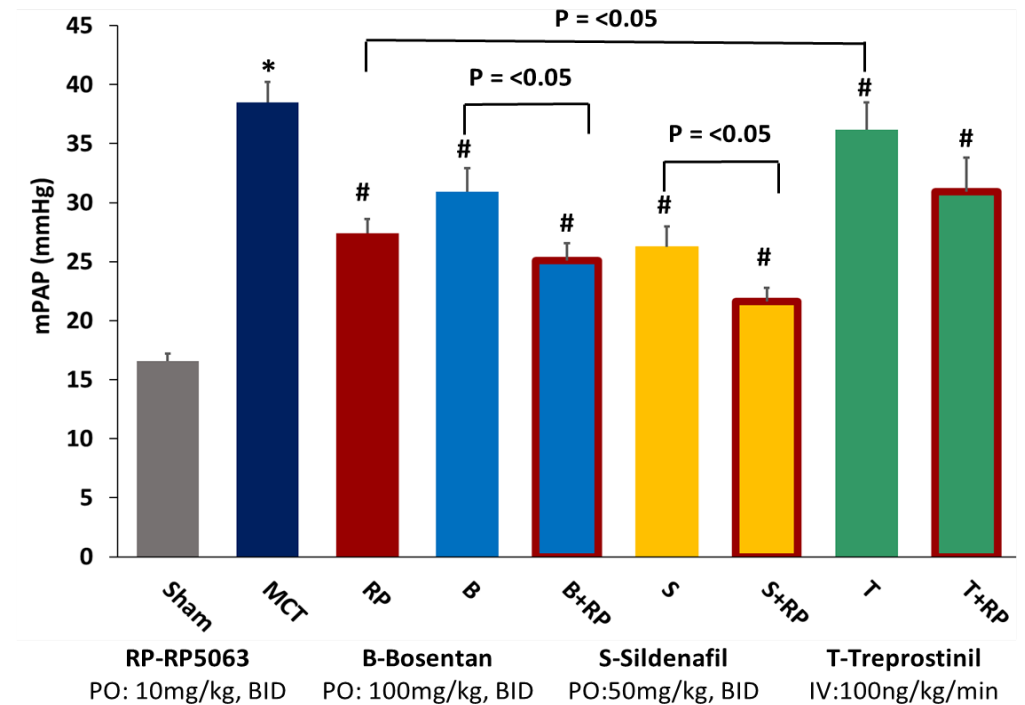
Brilaroxazine: Encouraging Results in PAH Translational Rodent Models

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



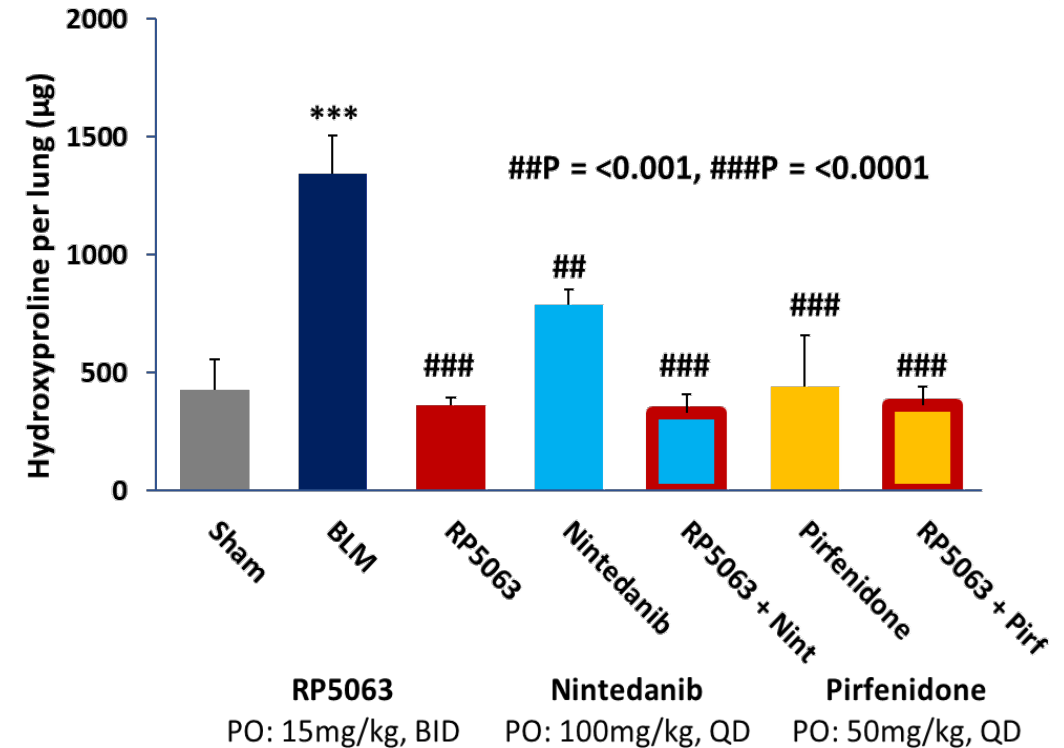
Brilaroxazine: Encouraging Results in Bleomycin-Induced IPF Rodent Model

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

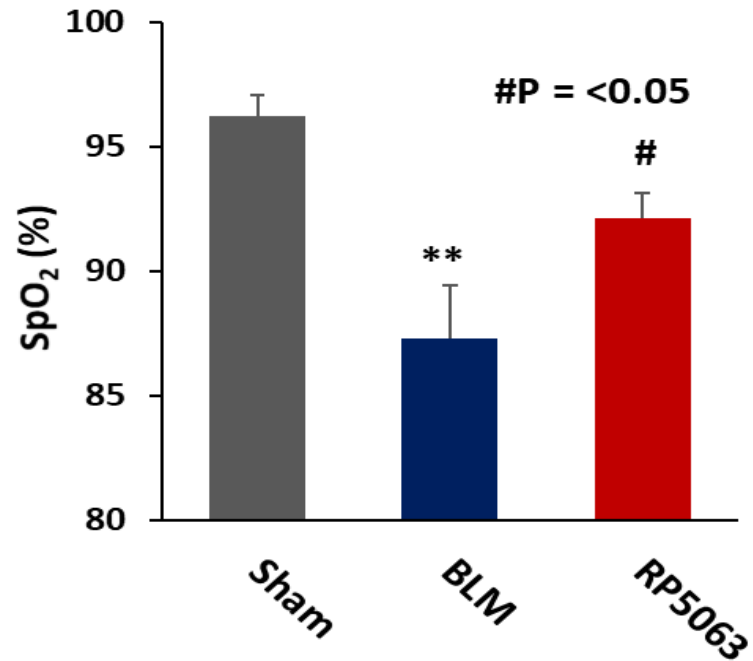
Brilaroxazine mitigates lung fibrosis / collagen (Decrease in Hydroxyproline)



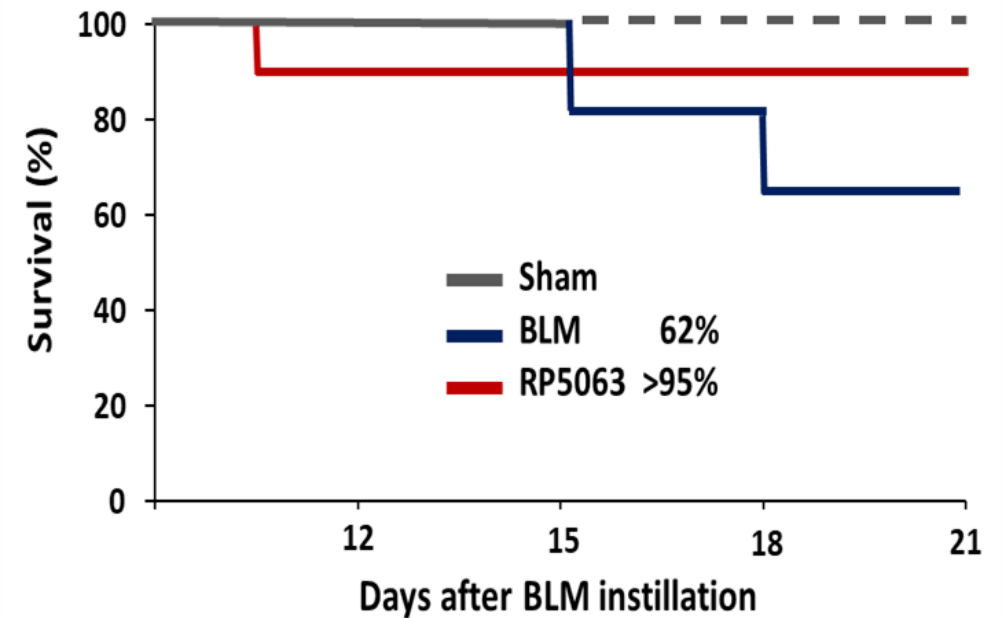
Brilaroxazine Improves Survival in Bleomycin Induced IPF Rodent Model

Significant Treatment Effect and Functional Outcomes

Brilaroxazine Mitigates Respiratory Resistance



Brilaroxazine Improves Survival



Brilaroxazine: Ready for Phase 2 Trials in PAH and IPF

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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