



Reviva Pharmaceuticals, Inc.

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Engineered neuroreceptor-specificity set to deliver next-generation schizophrenia therapeutics

Reviva Pharmaceuticals, a clinical-stage biopharmaceutical company, is focused on the development of next-generation neuroreceptor-targeting therapeutics to treat schizophrenia and other neuroreceptor-driven CNS, respiratory and metabolic diseases with high unmet needs.

Reviva Pharmaceuticals, a clinical-stage biopharmaceutical company based in Cupertino, California, USA, is applying a chemical genomics-powered technology platform supported by novel and proprietary chemistries to develop next-generation therapeutics for conditions of the central nervous system (CNS), and the respiratory and metabolic systems.

Since their introduction 70 years ago, CNS-targeting therapeutics have come a long way in terms of safety and efficacy. Most classes of CNS-targeting therapeutics, including antipsychotic drugs, are designed to modulate the activity of specific neurotransmitter receptors or neuroreceptors. First-generation antipsychotic drugs targeted dopamine 2 (D₂) receptors, but while very effective, their use was linked to high rates of undesirable systemic side-effects stemming from their interactions with the off-target receptors in different parts of the brain and/or from cross interactions with other neuroreceptors. Second-generation antipsychotics, developed to target both D₂ receptors and serotonin 5-HT_{2A} receptors, improved on the efficacy of the class and helped reduce the CNS side effects. While first and second-generation antipsychotics were designed to antagonize the target receptors, more recent third-generation antipsychotics aimed to partially agonize some of those receptors to reduce side effects and improve tolerability while maintaining the efficacy. However, antipsychotics still face significant patient compliance challenges due to the persistence of safety issues including neuroleptic, metabolic, cardiac, endocrine, and reproductive side effects caused by off-target activities.

Reviva's lead drug candidate, brilaroxazine (RP5063), is a multimodal modulator of the serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT₇ receptors and D₂, D₃, D₄ dopamine receptors in clinical development for multiple neuropsychiatric indications including schizophrenia, bipolar disorder, major depressive disorder (MDD), psychotic and agitation symptoms in dementia or Alzheimer's disease, Parkinson's disease psychosis, and attention deficit hyperactivity disorder (ADHD). Beyond its use in CNS disorders, brilaroxazine has also been granted an Orphan Drug designation by the U.S. Food and Drug Administration (FDA) for development in two respiratory indications in which serotonin signaling plays a central role in triggering pathology—pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF).

In addition to its clinical programs, Reviva is developing a range of preclinical programs focused on

NCE (Program)	Target indications	Stage
RP5063 (Neuro-psychiatric)	Schizophrenia	Phase 3
	Bipolar disorder	Phase 2
	Depression (MDD)	Phase 2
	Attention deficit hyperactivity disorder	Phase 2
	Parkinson's psychosis	Phase 2
	Alzheimer's psychosis and agitation	Phase 2
RP5063 (Pulmonary)	Pulmonary arterial hypertension (PAH)	Phase 2
	Idiopathic pulmonary fibrosis (IPF)	Phase 2
RP1208	Depression	Preclinical
	Obesity	Discovery

Fig. 1 | Reviva Pharmaceuticals' pipeline. Reviva has developed a broad pipeline of next-generation therapeutics for conditions of the central nervous system and the respiratory and metabolic systems based on the company's chemical genomics-powered technology platform and novel and proprietary chemistries.

indications in which neurotransmitter modulation could have therapeutic effects. The company's lead preclinical asset is RP1208, a new multimodal chemical entity for the treatment of depression and obesity (Fig. 1). The company holds composition of matter patents for both RP5063 and RP1208 in Europe, and in the United States, and other countries.

"Antipsychotics represent a class of CNS therapeutics with a great unrealized potential due to vexing side effects and suboptimal efficacies," said Laxminarayan Bhat, founder, President and CEO of Reviva. "Our strategy for tackling these issues consists of harnessing the power of chemical genomics to systematically address and reduce off-target receptor activities to mitigate adverse effects and increase target receptor specificity to optimize efficacy by fine-tuning the chemical structures of candidate small molecules. The resulting new chemical entities bring new hope for patients worldwide with substantial unmet needs."

The company's initial focus with brilaroxazine is on schizophrenia and associated neuropsychiatric comorbidities. Reviva is looking for strategic collaborations and partnerships for clinical development

and commercialization for its brilaroxazine program as well as for other partnership opportunities for its preclinical programs, including RP1208, in the areas of CNS, cardiovascular (CV), metabolic and inflammatory indications.

Schizophrenia—a highly unmet need

Schizophrenia is a chronic and debilitating mental illness that is estimated to affect about 1% of the world's population. Schizophrenia results from a combination of genetic factors, certain hereditary risks, and a complex pathology affecting different brain regions, neural pathways, neurochemistries, and cell receptors, that is not yet fully understood. Generally, the pathophysiology of schizophrenia is believed to be determined by imbalances in neurotransmitters, in particular dopamine and serotonin, and in four neural pathways in the brain, namely the mesocortical, nigrostriatal, mesolimbic and tuberoinfundibular pathways.

Schizophrenia usually presents as a combination of cognitive, behavioral and emotional symptoms that results in an inability to function normally. Symptoms typically involve delusions, hallucinations or disorganized speech, and are commonly mistaken with multiple personality disorder.

For diagnostic purposes, schizophrenia symptoms are categorized into positive, negative, depression and cognitive symptoms. Positive symptoms are those that present with the illness such as hallucinations and delusions; negative symptoms refer to normal behaviors, such as the ability to express emotions, show empathy, communicate verbally, and engage with others, that are hindered with onset of the illness; cognitive symptoms include impairments in attention, working memory or executive function.

The treatment of schizophrenia is typically multipronged, including both pharmacological and non-pharmacological strategies. A common approach consists of combining psychotherapy with a carefully managed regimen of antipsychotic drugs to achieve overall symptom reduction, prevent relapses, and regain normal social functioning.

A key challenge for the development of novel therapeutics in schizophrenia is the assessment of the clinical efficacy of a treatment given the wide range of individual presentations. To standardize the evaluation of new treatments, frameworks have been established such as the Positive and Negative Syndrome Scale (PANSS), an interval scale that helps quantify the patient's experience across 30 positive, negative and general symptoms.

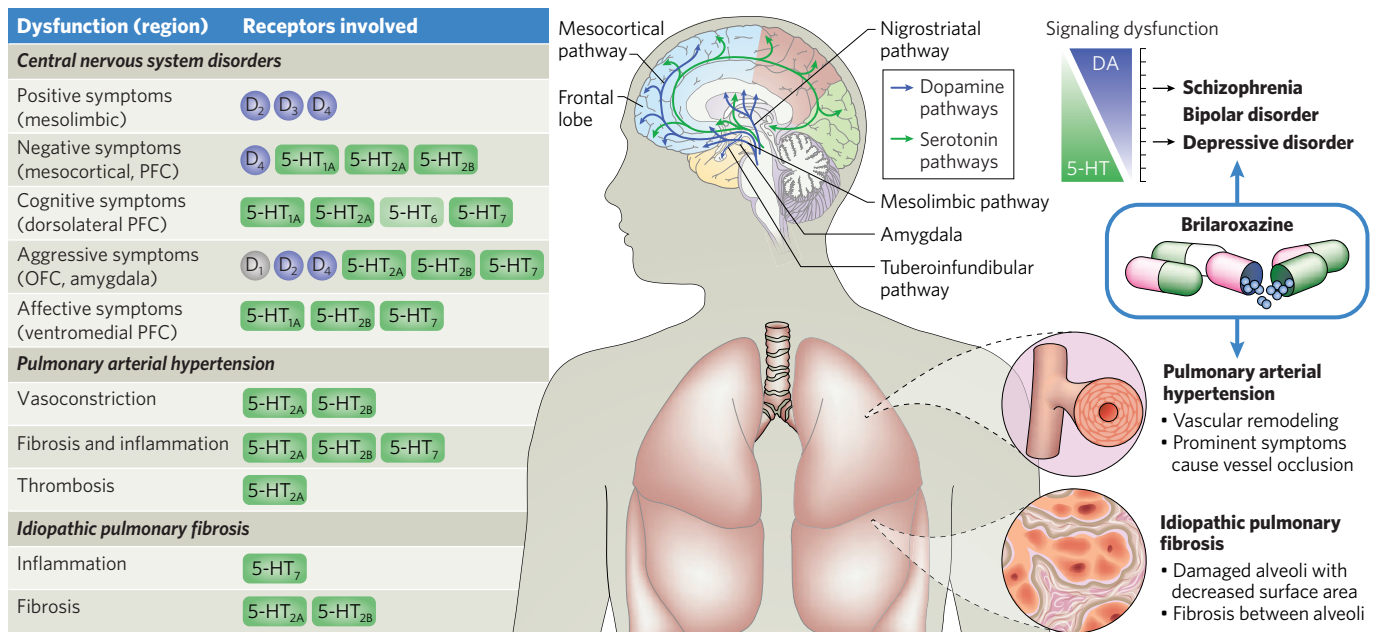


Fig. 2 | The mechanistic connection between neuropsychiatric disorders and interstitial lung diseases. Analogous dysfunctional dopamine and serotonin receptor signaling processes occurring in the brain have been implicated in the pathogenesis of schizophrenia and other neuropsychiatric disorders, and serotonin receptor signaling processes in the pathogenesis of lung conditions such as pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF), respectively. OFC, orbitofrontal cortex; PFC, prefrontal cortex.

"There are no therapies available that adequately address the complex mix of positive and negative symptoms, mood, and cognitive impairment associated with schizophrenia," said Bhat. "With an estimated 30–50% rate of treatment discontinuation among acute patients and 42–74% among stable patients due to suboptimal efficacy and side effects such as drug-induced movement disorders, obesity, diabetes, and even sexual dysfunction caused by existing antipsychotic treatments, the search for better therapeutic options is ongoing. At Reviva we are focused on developing a drug that targets both the serotonin and dopamine receptor signaling systems to more effectively treat schizophrenia and its comorbid symptoms."

Brilaroxazine—delivering new hope for schizophrenia

Existing antipsychotics present a set of side effects almost as diverse as the underlying schizophrenia symptomatology, resulting in low patient compliance rates. Mechanistically, the side effects are due to promiscuity among existing antipsychotics for neuroreceptors throughout the brain beyond the dopamine and serotonin receptors involved in the etiology of schizophrenia.

Reviva's brilaroxazine is a multimodal modulator of serotonin and dopamine receptors that helps stabilize the serotonin/dopamine system, a key determinant of the pathogenesis of schizophrenia and other associated neuropsychiatric disorders (Fig. 2). Brilaroxazine exhibits high binding affinity for the D₂, D₃, D₄, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT₇ receptors (K_i ≤ 6 nM), and moderate binding affinity for the serotonin transporter (SERT), 5-HT₆ receptor, and the nicotinic acetylcholine receptor α₂ (K_i ≤ 50 nM).

In a phase 1a clinical trial with healthy subjects, brilaroxazine exhibited a favorable safety profile, and in a phase 1b trial with stable schizophrenia patients—patients with mild symptoms—brilaroxazine elicited

a statistically significant PANSS improvement over placebo. A phase 2 randomized, double blind, placebo-controlled, multi-center safety and efficacy trial of brilaroxazine in acute schizophrenia patients—patients who are experiencing severe symptoms—also showed significant PANSS total score reduction over placebo and, in addition, significantly higher compliance rates. No cardiometabolic, cardiovascular, prolactin or endocrine complications were recorded compared to placebo. Based on these favorable results, the FDA has provided Reviva with guidance for a potential 'superior safety' label claim.

Reviva is now planning to initiate phase 3 clinical studies with brilaroxazine in schizophrenia patients in H2-2021.

"We are excited to be entering the final stretch of clinical testing for brilaroxazine with guidance for a superior safety label claim from the FDA," said Bhat. "We see this as a first step toward opening new therapeutic possibilities for patients suffering a broad spectrum of psychotic disorders and lacking safe therapeutic options."

Brilaroxazine is broadly applicable in multiple psychotic indications because these diseases are often comorbid and exist on a continuum of dopamine and serotonin signaling dysfunction. On this continuum, schizophrenia is on the dopamine end, bipolar disorder places somewhere in the middle, and MDD is on the serotonin end. The clinical development of brilaroxazine for bipolar disorder and MDD should follow an accelerated timeline based on the phase 1 safety work already conducted for schizophrenia.

Expanding the therapeutic potential of neurotransmitter modulators

Beyond their role in neurological homeostasis, neurotransmitters play other key physiological roles in the body that make them other optimal targets for treating certain non-neurological conditions. Reviva is exploring the use of brilaroxazine in PAH and IPF, two disorders characterized by lung tissue

remodeling due to inflammation, proliferation of fibrosis, microthrombi and pulmonary hypertension. At the physiological level, serotonin signaling is involved in modulating the inflammatory and fibrotic mechanisms underlying vasoconstriction and thrombosis (Fig. 2).

Reviva is evaluating the serotonin receptor-antagonizing ability of brilaroxazine, in particular of the 5-HT_{2A}, 5-HT_{2B}, and 5-HT₇ receptors, as a potential treatment for PAH and IPF. In vivo studies have shown brilaroxazine to be equivalent or superior compared to current first-line treatments and, notably, without the cardiac side effects commonly encountered in those treatments. Based on these studies, the FDA has granted an Orphan Drug Designation to brilaroxazine for the treatment of PAH and IPF. With the route of administration and dosing frequency being the same as for schizophrenia, phase 2 trials with brilaroxazine for PAH and IPF are in preparation based on the favorable phase 1b and phase 2 human studies in schizophrenia.

"We are only now starting to harness the potential of targeting neurotransmitter homeostasis for therapeutic applications beyond neurological disorders," said Bhat. "Reviva is leading these efforts by using its unique approach to engineering novel compounds of exquisite specificity and high efficacy. We are keen to expand on these efforts in collaboration with partners worldwide interested in developing next-generation neuroreceptor-targeting therapeutics to improve the lives of patients around the globe."

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