Reviva Pharmaceuticals Announces Presentation of Clinical Pharmacology Studies Data on Brilaroxazine at the ASPET 2023 Annual Meeting

Data reinforce brilaroxazine's differentiated clinical pharmacology and safety profile

Brilaroxazine may be co-administered with other drugs metabolized by CYP3A inhibitors

Metabolism and excretion profiles of brilaroxazine were similar across mice, canines, and humans

CUPERTINO, Calif., May 22, 2023 — Reviva Pharmaceuticals Holdings, Inc. (NASDAQ: RVPH) ("Reviva" or the "Company"), a clinical-stage pharmaceutical company developing therapies that seek to address unmet medical needs in the areas of central nervous system (CNS), respiratory and metabolic diseases, has presented two posters on promising clinical pharmacology and safety studies data on the novel serotonin-dopamine stabilizer brilaroxazine at the American Society for Pharmacology and Experimental Therapeutics (ASPET) 2023 annual meeting took place in St. Louis, Missouri, USA, May 18-21, 2023. The ASPET posters are available at revivapharma.com/publications. Brilaroxazine is currently in phase 3 clinical trials for schizophrenia and topline data from the pivotal phase 3 is anticipated in mid this year.

"We were pleased to present data in humans and animals further characterizing the differentiated pharmacological and safety profile, and predictable pharmacokinetics (PK), metabolism and excretion profiles of brilaroxazine at this year's ASPET meeting," said Laxminarayan Bhat, Ph.D., Founder, President, and CEO of Reviva. "These data support the concomitant use of brilaroxazine with other medications metabolized by CYP3A4 as most schizophrenia patients take multiple concomitant medications. Importantly, brilaroxazine has demonstrated similar metabolism, and excretion profiles in humans and preclinical species canines and mice which further support brilaroxazine's differentiated safety profile."

Key poster highlights support brilaroxazine's differentiated clinical pharmacology and safety profile:

- *CYP3A inhibition and induction exert limited effects on brilaroxazine pharmacokinetics*
  CYP3A4 metabolizes several standard of care antipsychotics (e.g., aripiprazole, lurasidone, risperidone, quetiapine, cariprazine, brexpiprazole, lumetaperone, and clozapine) which often leads to significant plasma drug concentration changes when co-administered with another drug metabolized by CYP3A4 inhibitors or inducers due to drug-drug interactions and changes efficacy and side effect profiles. As part of the required clinical studies for New Drug Application (NDA), the drug-drug interactions between brilaroxazine with a strong CYP3A4 inhibitor (itraconazole) and inducer (phenytoin) were evaluated.

- Brilaroxazine can be co-administered with itraconazole, and other drugs metabolized by strong CYP3A inhibitors
  - Brilaroxazine single dose co-administered with itraconazole at steady-state resulted in a slight increase of 8, 15 and 13% in brilaroxazine Cmax, AUC0-t, and AUC0- , respectively.
  - No notable difference in brilaroxazine's mean elimination half-life existed between brilaroxazine administered alone and concomitantly with itraconazole. These findings suggest that the drug-drug interaction between itraconazole and brilaroxazine is not clinically significant.
- Phenytoin (a strong CYP3A4 inducer) decreased brilaroxazine exposure by approximately 50%, suggesting brilaroxazine dose modification may be needed when co-administering with phenytoin and other strong CYP3A inducers
  - Brilaroxazine single dose co-administered with phenytoin at steady-state resulted in decrease of ~33%, 57% and 54% in brilaroxazine Cmax, AUC0-t, and AUC0 , respectively.
  - These findings suggest a potentially clinically significant drug-drug interaction between phenytoin (a strong CYP3A inducer) and brilaroxazine.

- *Brilaroxazine pharmacokinetics, metabolism, and excretion profile in humans and animals*

  Brilaroxazine's predictable PK profile with daily doses up to 100 mg allowing for once daily dosing has been defined in clinical studies including a single ascending dose (SAD) study in normal healthy volunteers, multiple ascending dose study in patients with stable schizophrenia, and Phase 2 study data from individuals with acute schizophrenia or schizoaffective disorder. As part of the required studies for New Drug Application (NDA), brilaroxazine's single-dose pharmacokinetics, metabolism, and excretion (PME) profiles were evaluated in humans and animals.
  - Metabolism and excretion profiles are similar among all three species following a single oral dose of [14C]-brilaroxazine
    - Total recovery at 86.1% in humans, 88.2% in mice, and 77.8% in canines
  - Feces represent the predominant route of excretion in all species
  - M219 is the major circulating metabolite and M465a is the major excreted metabolite in all species
  - No human-specific metabolite was detected in plasma
  - The emergent metabolic pathways for all species involve oxidation, N- or O-dealkylation with subsequent sulfation and/or conjugation with glucuronic acid

About Drug-Drug Interaction (DDI) Clinical Studies

Drug-drug interaction (DDI) clinical studies are an imperative step in the new drug approval process. DDI studies help identify potential adverse reactions that may be caused by interactions between multiple drugs, leading to unintended reactions, toxic side effects, or in some cases, a lack of therapeutic efficacy. With the rise in polypharmacy to treat

comorbidities, alongside prevalent substance abuse, drug-drug interactions have become a critical factor to consider when treating schizophrenia. Approximately 50% of prescribed drugs and over 25% of antipsychotics currently on the market are known to cause drug interactions with CYP3A4 inhibitors and can lead to side effects. Findings from DDI studies help to inform drug labeling that is then used by healthcare providers to aid in therapeutic decision-making.

About Brilaroxazine

Brilaroxazine is a new chemical entity with potent affinity and selectivity against key serotonin and dopamine receptors implicated in schizophrenia and its comorbid symptoms. In a multinational, multicenter, double-blind Phase 2 study in 234 patients with acute schizophrenia or schizoaffective disorder, brilaroxazine met its primary endpoint, reducing Positive and Negative Syndrome Scale (PANSS) total score and demonstrating statistically significant improvement of overall drug treatment outcomes using Clinical Global Impression (CGI) scale and for secondary endpoints evaluating social functioning, and positive and negative symptoms, and directional improvements for depression and cognition. In this completed Phase 2 study, brilaroxazine met all safety endpoints with no weight gain, no increase in blood sugar and lipids, and no cardiac or endocrine adverse effects compared to placebo. Positive data from a clinical drug-drug interaction (DDI) study investigating the potential effect of CYP3A4 enzyme on brilaroxazine in healthy subjects supports no clinically significant interaction when combined with a CYP3A4 inhibitor. A full battery of regulatory compliant toxicology and safety pharmacology studies has been completed for brilaroxazine. The U.S. Food and Drug Administration (FDA) has agreed to consider a potential superior safety label claim if there is a positive outcome on a relevant endpoint in a pivotal Phase 3 study in patients with schizophrenia. Reviva intends to develop brilaroxazine for other neuropsychiatric indications including bipolar disorder, major depressive disorder (MDD) and attention-deficit/hyperactivity disorder (ADHD).

Additionally, brilaroxazine has shown promising efficacy for pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF) with mitigation of lung fibrosis and inflammation in translational animal models. Reviva believes brilaroxazine has the potential to delay disease progression in PAH and IPF and intends to develop brilaroxazine for these pulmonary indications. Brilaroxazine has already received Orphan Drug Designation by the U.S. FDA for the treatment of these conditions.

To learn more about the clinical and preclinical data available for brilaroxazine, please visit revivapharma.com/publications.

About Reviva

Reviva is a clinical-stage biopharmaceutical company that discovers, develops, and seeks to commercialize next-generation therapeutics for diseases representing unmet medical needs and burdens to society, patients, and their families. Reviva’s current pipeline focuses on the

central nervous system, respiratory and metabolic diseases. Reviva's pipeline currently includes two drug candidates, brilaroxazine and RP1208. Both are new chemical entities discovered in-house. Reviva has been granted composition of matter patents for both brilaroxazine and RP1208 in the United States (U.S.), Europe, and several other countries.

Forward-Looking Statements

This press release 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 the Private Securities Litigation Reform Act, as amended, including those relating to the Company's RECOVER Phase 3 trial, including expectations therefor and the timing of topline data, the Company's expectations regarding the anticipated clinical profile of its product candidates, including statements regarding anticipated efficacy profile, product development, clinical and regulatory approval pathways, timelines expenses, market opportunity, ability to raise sufficient funding, competitive position, possible or assumed future results of operations, business strategies, potential growth 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 our financial performance and involve known and unknown risks, uncertainties, and other factors 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 press release. 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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