

PharmaTher Enters into Exclusive Option Agreement with Case Western Reserve University to Develop and Commercialize Ketamine for Rett Syndrome

TORONTO, November 1, 2022 -- PharmaTher Holdings Ltd. (the “Company” or “PharmaTher”) (OTCQB: PHRRF) (CSE: PHRM), a specialty pharmaceutical company focused on developing and commercializing novel uses and delivery forms of ketamine to treat mental health, neurological and pain disorders, is pleased to announce that the Company has entered into an evaluation and exclusive option agreement (the “Agreement”) with Case Western Reserve University (“CWRU”) in the development and commercialization for the intellectual property of ketamine in the treatment Rett Syndrome, a rare genetic neurological disorder. Ketamine has been subject to a Phase 2 clinical trial ([NCT03633058](#)) for Rett syndrome and unpublished results will be evaluated to support a defined clinical and regulatory plan for FDA feedback.

“We are pleased to have added the Rett syndrome program to our clinical stage product pipeline that focuses on novel uses and delivery forms of ketamine in the treatment of mental health, neurological and pain disorders,” said Fabio Chianelli, CEO of PharmaTher. “In research, ketamine has shown the potential for treating Rett syndrome. We will work with CWRU and the clinical trial team in pursuing discussions with the FDA to determine all regulatory and clinical options that could expedite the pathway towards having ketamine available for Rett syndrome patients.”

Currently, there is no known cure or FDA-approved drugs for treating Rett syndrome. According to the Rett Syndrome Foundation, Rett syndrome is a rare genetic neurological disorder that occurs almost exclusively in girls. It leads to severe impairments in their ability to speak, walk, eat, and even breathe easily. Prominent features of Rett syndrome include near constant repetitive hand movements and loss of purposeful hand use. Rett syndrome is usually recognized in children between 6 to 18 months. Rett syndrome is caused by mutations on the X chromosome on a gene called MECP2. Rett syndrome occurs worldwide in 1 of every 10,000 female births, and is much rarer in boys.

Ketamine has the potential to treat Rett syndrome, which has been independently validated in two different laboratories in two different strains of *Mecp2* mice and has completed a Phase 2 clinical trial with Rett syndrome, with results not published. The therapeutic potential of ketamine for treating Rett syndrome was first demonstrated by Dr. David M. Katz, Professor Emeritus, Department of Neurosciences, School of Medicine at CWRU, and colleagues, who found that treatment of heterozygous female *Mecp2* mutant mice with a subanesthetic dose of ketamine (8 mg/kg) acutely reversed abnormalities in Fos expression and sensorimotor function [[1](#)]. Chronic

administration of ketamine was also found to improve symptoms and extend lifespan in null male *Mecp2* mutants [2]. The ability of low-dose ketamine to improve function across a broad range of symptoms may be related to its ability to increase cortical network activity, possibly by selective inhibition of GABAergic interneurons [3], as well as to decrease synaptic excitability in brainstem networks important for respiratory and autonomic control [4]. Thus, ketamine may be ideally suited to redress the imbalance between cortical and brainstem activity that characterizes the MeCP2-deficient brain. Moreover, in addition to its acute effects on circuit function, work in other disease models has shown that ketamine also rapidly stimulates dendritic growth, BDNF levels, and expression of key synaptic proteins [5, 6], at least in part through activation of mTOR signaling, which is deficient in *Mecp2* mutants [7]. These findings suggest that, in addition to acute rescue of neurological function, ketamine also has the potential to promote synaptic repair in Rett syndrome by enhancing structural and functional connectivity, as previously shown in animal models of depression and stress [8].

Under the terms of the Agreement, PharmaTher gained an exclusive option for up to 12 months to evaluate the regulatory, clinical development and commercialization plan for CWRU's intellectual property portfolio, which includes, US issued patent no. 11,213,494 and US provisional patent no. 62/312,749 entitled, "Composition and method for the treatment of pervasive development disorders", and US provisional patent no. 62/004,695 entitled, "Acute and sustained effects of low-dose ketamine treatment in mouse models of Rett Syndrome." Consistent with industry standards, PharmaTher paid a one-time fee for entering into the Agreement, and should the Company elect to exercise its option, both the Company and CWRU will negotiate a license agreement.

About PharmaTher Holdings Ltd.

PharmaTher Holdings Ltd. (OTCQB: PHRRF) (CSE: PHRM) is a specialty pharmaceutical company focused on developing and commercializing novel uses and delivery forms of ketamine to treat mental health, neurological and pain disorders. PharmaTher's product portfolio consists of KETARX™ (ketamine) delivered by intravenous injection, intradermal microneedle patch, and subcutaneous pump administration. Learn more at PharmaTher.com.

For more information about PharmaTher, please contact:

Fabio Chianelli
Chief Executive Officer
PharmaTher Holdings Ltd.
Tel: 1-888-846-3171
Email: info@pharmather.com
Website: www.pharmather.com

Neither the Canadian Securities Exchange nor its Regulation Services Provider have reviewed or accept responsibility for the adequacy or accuracy of this release.

Cautionary Statement

This press release contains 'forward-looking information' within the meaning of applicable Canadian securities legislation. These statements relate to future events or future performance. The use of any of the words "could", "intend", "expect", "believe", "will", "projected", "estimated", "potential", "aim", "may" and similar expressions and statements relating to matters that are not historical facts are intended to identify forward-looking information and are based on PharmaTher Holdings Ltd. (the "Company") current belief or assumptions as to the outcome and timing of such future events. Forward-looking information is based on reasonable assumptions that have been made by the Company at the date of the information and is subject to known and unknown risks, uncertainties, and other factors that may cause actual results or events to differ materially from those anticipated in the forward-looking information. Given these risks, uncertainties and assumptions, you should not unduly rely on these forward-looking statements. The forward-looking information contained in this press release is made as of the date hereof, and Company is not obligated to update or revise any forward-looking information, whether as a result of new information, future events or otherwise, except as required by applicable securities laws. The foregoing statements expressly qualify any forward-looking information contained herein. Factors that could cause actual results to differ materially from those anticipated in these forward-looking statements are described under the caption "Risk Factors" in Company's management's discussion and analysis for the period August 31, 2022 ("MD&A"), dated November 25, 2022, which is available on the Company's profile at www.sedar.com.

This news release does not constitute an offer to sell or the solicitation of an offer to buy, and shall not constitute an offer, solicitation or sale in any state, province, territory or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state, province, territory or jurisdiction.