PharmaTher Holdings Submits for FDA Orphan Drug Designation for Ketamine to Treat Rett Syndrome

TORONTO, Jan. 18, 2023 -- PharmaTher Holdings Ltd. (the “Company” or “PharmaTher”) (OTCQB: PHRRF) (CSE: PHRM), a leader in specialty ketamine pharmaceuticals, is pleased to announce that it has applied with the U.S. Food and Drug Administration (“FDA”) to receive Orphan Drug Designation (“ODD”) for ketamine to treat Rett Syndrome, a rare genetic neurological disorder. Ketamine has been subject to a Phase 2 clinical trial (NCT03633058) for Rett syndrome. Unpublished results from this study will be evaluated to support a potential Phase 3 clinical study and FDA agreement on a regulatory plan for approval which the Company may pursue.

PharmaTher currently holds four orphan drug designations granted by the FDA for KETARX™ (racemic ketamine), which include:

1. Prevention of Ischemia-reperfusion injury from organ transplantation;
2. Treatment of Status Epilepticus;
3. Treatment of Amyotrophic Lateral Sclerosis; and
4. Treatment of Complex Regional Pain Syndrome.

“We are focused on unlocking ketamine’s potential for rare disorders, and the addition of the Rett syndrome program to our FDA-approved orphan drug designation pipeline strengthens our position in leading the potential use of ketamine for unmet medical needs in mental health, neurological and pain disorders,” said Fabio Chianelli, CEO of PharmaTher.

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 signalling, 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].

The Orphan Drug Act grants special status to a drug or biological product to treat a rare disease or condition upon request of a sponsor. This status is referred to as orphan designation (or sometimes “orphan status”). The FDA grants orphan status to products that treat rare diseases, providing incentives to sponsors developing drugs or biologics. The FDA defines rare diseases as those affecting fewer than 200,000 people in the United States at any given time. Orphan drug designation would qualify ketamine for certain benefits and incentives, including seven years of marketing exclusivity if regulatory approval is ultimately received for the designated indication, potential tax credits for certain clinical drug testing costs, eligibility for orphan drug grants, and the waiver of the FDA New Drug Application filing fee of approximately $2.4 million.

The Company previously announced that it has entered into an evaluation and exclusive option agreement (the “Agreement”) with Case Western Reserve University in the development and commercialization of the intellectual property of ketamine in the treatment of Rett Syndrome.

About PharmaTher Holdings Ltd.

PharmaTher Holdings Ltd. (OTCQB: PHRRF) (CSE: PHRM) is a specialty pharmaceutical company focused on developing and commercializing KETARX™ (racemic ketamine) delivered by intravenous injection, microneedle patch, and on-body pump for mental health, neurological and pain disorders. Learn more at **PharmaTher.com**.

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