PharmaTher Announces Positive Results from Study of KETABET™ for Depression

KETABET™ (Ketamine and Betaine) shown effectiveness as measured by the Clinician Administered Dissociative States Scale

Study results are adequate to give an effect size in powering a placebo-controlled clinical study

PharmaTher planning a Phase 2 clinical study to incorporate KETABET™ in its proprietary microneedle patch for depression

TORONTO, June 07, 2022 -- PharmaTher Holdings Ltd. (the "Company" or "PharmaTher") (OTCQB: PHRRF) (CSE: PHRM), a leader in specialty ketamine pharmaceuticals, is pleased to announce positive results from an investigator-led observational study (the "Study") evaluating the impact of KETABET™, a patented drug combination of FDA-approved ketamine and betaine anhydrous, on the unwanted ketamine side effects seen post ketamine treatment for subjects with depression. KETABET™ aims to prevent the potential adverse psychiatric effects of repeated ketamine treatment for depression and other indications, including suicidal ideation, substance abuse, post-traumatic stress disorder, and chronic pain.

The investigator-led observational study is a randomized crossover study with subjects suffering from unmanageable depression and currently receiving ketamine treatment but experiencing unwanted side effects of ketamine. The study enrolled 10 subjects and aimed to determine if the administered oral betaine anhydrous before ketamine treatment can reduce some or all of the unwanted side effects observed in the first few hours of ketamine therapy as determined by the Clinician Administered Dissociative States Scale ("CADDS"). Alleviation or reduction of side effects would support further progression of this product strategy. The CADDS is currently the standard scale used for studies assessing acute psychoactive effects of ketamine. It is used to measure present-state dissociative symptoms and assess treatment-emergent dissociative symptoms. The CADDS is comprised of 23 questions each evaluated on a 5-point scaling system (0 = "not at all", 1 = "mild", 2 = "moderate", 3 = "severe", and 4 = "extreme"). Assessment is based on three components, including depersonalization, derealization and amnesia, and an overall total score representing the severity of the condition. Depersonalization is a state in which one loses a sense of identity relative to thoughts and feelings. Derealization is a state where one feels detached from their surroundings.

The Study's data support the benefit of pre-treatment with oral anhydrous betaine prior to ketamine administration for certain side effects measured by CADDS, including depersonalization and derealization. A reduction in mean of 66% at 40 minutes following ketamine infusion initiation was seen for each of these measures in the Study. Ketamine and betaine were well tolerated with no serious adverse events reported. Although the Study was not meant for statistical significance, it supports the Company's planned placebo-controlled phase 2 clinical study incorporating KETABET™ in the Company's proprietary microneedle patch and will further evaluate betaine anhydrous dose, timing of pre-treatment, and duration of effect on depersonalization and derealization effects of low-dose ketamine. Reduction in the depersonalization and derealization side effects associated with low-dose ketamine infusion will potentially improve treatment compliance, treatment dose range, and treatment duration associated with ketamine therapy. Additional influence of pre-treatment with betaine prior to low-dose ketamine administration will further define the Company's KETABET™ product scope for this and potentially other indications. Complete results of the Study are expected to be submitted for presentation at a medical congress by 2H-2022.

Dr. Raul Cruz, MD, Principal Investigator of the Study, commented: "The results of this pilot observational study were very promising as the pre-treatment with betaine prior to ketamine administration demonstrated a better recovery from ketamine effects and higher dose tolerability for patients that typically experience dose limiting side effects. In general, patients that typically experienced nausea during treatment had a notable reduction and improved recovery. We are encouraged by the increase in alertness and decreased dizziness with pre-treatment of betaine and look forward to incorporating this combination into our practice for patients that require ketamine therapy for depression."

Fabio Chianelli, CEO of PharmaTher, commented: "We are very pleased with the results from this Study as it provides support for advancing our microneedle patch program in a potential Phase 2 clinical study evaluating KETABET™ for mental health and pain disorders."

Based on the Study results, the Company is preparing to engage the FDA to establish the next steps for a planned Phase 2 clinical study to allow for KETABET™ evaluation in depression under the 505(b)(2) regulatory pathway. The Company intends to use its proprietary hydrogel-forming microneedle patch for the planned Phase 2 clinical study.

Granted patents of KETABET™ are issued in the U.S. (Patent No. 11,213,495), Japan (Patent no. 6967532) and Taiwan (Patent no. I648049). The Company expects to convert the current patent applications in Europe, Canada, Israel and China into granted patents. Patent protection is expected to expire in 2036.

Potential of KETABET™

KETABET™, a patented drug combination of FDA-approved ketamine and betaine anhydrous, has been shown in research to enhance the antidepressant effect while having the potential to reduce the known negative side effects of ketamine

significantly.[1] Side effects such as hallucinations, confusion, memory loss and abuse liability compromise the compliance and potential therapeutic value of ketamine.[2] The combination of ketamine and betaine anhydrous produced more robust antidepressant-like responses than their individual effects and that the combination blocked the psychotomimetic effects of ketamine.[1] This suggests that betaine anhydrous can be considered as an add-on therapy to ketamine or as a fixed-dose combination therapy for treatment-resistant depression, treatment-resistant bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder and chronic pain.

More than 300 million people suffer from major depressive disorder and 100 million people are resistant to available treatments worldwide. Ketamine is emerging as a viable treatment option for depression. Recent clinical studies have shown that low dose ketamine produces a rapid-acting and sustained antidepressant effect in major depressive disorder,[3] bipolar depression,[4] depression with suicidal ideation[5] and post-traumatic stress disorder.[6] Despite this, the potential for abuse and misuse of ketamine and the adverse mental effects of ketamine leads to its limited clinical use and discontinuation.

Betaine anhydrous (CYSTADANE®) was approved by the FDA in 1996 to treat homocystinuria to decrease elevated homocysteine blood concentrations. There is growing evidence that betaine plays a critical role in regulating brain functions and has an antidepressant-like effect.[7] Betaine has been reported to prevent seizures in rodents,[8] to improve symptoms of Rett syndrome,[9] and to delay the onset of neurologic impairment due to vitamin B12 deficiency[10] clinically. Furthermore, betaine attenuates memory deficits induced by homocysteine.[11]

Potential of the Hydrogel-forming Microneedle Patch

The Company's patented hydrogel-forming microneedle ("MN") patch aims to deliver ketamine and KETABET™ for intradermal administration to treat various mental health, neurological and pain disorders. The MN patch consists of hydrogel-forming microneedle arrays and an accompanying reservoir that will overcome limitations by the quantity of drug loaded into the needles or onto the needle surfaces. As such, the MN patch can significantly increase the amount of drug that can permeate through the microneedle array and into the skin.[12] The MN patch is specifically tailored for ketamine and KETABET™ due to the volume of drug that is required to maximize their therapeutic utility and increase potential market opportunities.

The KETABET™ MN patch aims to empower patients to dose their medication remotely, safely and conveniently rather than being supervised by a healthcare provider at a certified medical office. KETABET™ MN patch has the potential for enabling continuous delivery of KETABET™ (without pain) with minimal formulation manipulation into systemic circulation while maintaining constant plasma levels for more than 24 hours that will improve efficacy and compliance for patients.[12-13] Also, PharmaTher's KETABET™ MN patch will incorporate anti-tampering and anti-abuse features that parallel the approach used by commercially available tamper-resistant transdermal fentanyl patches.

About PharmaTher Holdings Ltd.

PharmaTher Holdings Ltd. (OTCQB: PHRRF) (CSE: PHRM) is focused on the development and commercialization of specialty ketamine pharmaceuticals for mental health, neurological, and pain disorders. Learn more at **PharmaTher.com.**

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