PharmaTher Granted New Japanese Patent for KETABET™ (Ketamine Combination Formulation), Strengthening Global Patent Portfolio

TORONTO, November 30, 2021 -- PharmaTher Holdings Ltd. (the "Company" or "PharmaTher") (OTCQB: PHRRF) (CSE: PHRM), a clinical-stage psychedelics biotech company, is pleased to announce that the Japan Patent Office has issued Japanese Patent No. 6967532 for KETABET™, a combination formulation of FDA-approved ketamine and betaine anhydrous, which has shown in research to enhance the antidepressant effect while having the potential to reduce the known negative side effects of ketamine significantly. The granted patent strengthens the Company's global patent portfolio and it provides for broad potential of KETABET™ for uses in various mental health, neurological and pain disorders, as well as novel delivery forms such as with the Company's patented hydrogel-forming microneedle patch delivery system.

The patent titled: 'Method and Composition for Decreasing the Psychotomimetic Side Effect and Addictive Disorder of Ketamine' is expected to provide protection into 2036. Patent families protecting KETABET™ under an exclusive worldwide license agreement with the National Health Research Institutes have also been issued in Taiwan (Patent no. I648049), and the Company expects to convert the current patent applications in the U.S., Europe, Japan, Canada, Israel and China into granted patents.

"We are extremely pleased about the grant of this patent by the Japanese Patent Office as it validates the novelty and potential of KETABET™ for unmet medical needs, strengthens our global patent portfolio of novel ketamine solutions, provides confidence in expanding our patent coverage in major markets such as the U.S., and increases our ability to enter into potential new commercial partnerships for KETABET™ in Japan and major international markets," stated Fabio Chianelli, Chief Executive Officer of PharmaTher.

Potential of KETABET™

KETABET™, a patented combination formulation 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 a clinical-stage psychedelics biotech company focused on the research, development and commercialization of novel uses, formulations and delivery methods of psychedelics, such as ketamine, to treat mental health, neurological and pain disorders. PharmaTher is currently advancing an FDA approved phase 2

clinical study with ketamine to treat Parkinson's disease and is developing a novel microneedle patch for the intradermal delivery of psychedelics and infectious disease treatments.

Learn more at: **PharmaTher.com** and follow us on **Twitter** and **LinkedIn**.

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3. *Murrough et al. 2013; Wan et al. 2014*
4. *Ionescu et al. 2015; Nugent et al. 2014; Rybakowski et al. 2013*

5. *Aligeti et al. 2014; Thakurta et al. 2012; Zigman and Blier 2013*

6. *Feder et al. 2020*

7. *Freed 1984; 1985*

8. *Kim et al. 2013; Di Pierro et al. 2015*

9. *Percy and Lane 2005*

10. *van der Westhuyzen and Metz 1984*

11. *Chai et al. 2013*

12. *Donnelly R.F. Hydrogel-forming microneedles prepared from "super swelling" polymers combined with lyophilised wafers for transdermal drug delivery. PLoSONE. 2014 doi: 10.1371/journal.pone.0111547.*

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