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Pasithea Therapeutics Announces Preclinical Data that Shows PAS-004 Inhibits ETS2 Signaling, a Key Driver of Inflammation in IBD and Other Large Addressable Market Diseases

-- Demonstrates PAS-004's potential as a differentiated MEK inhibitor for immune-mediated inflammatory diseases such as IBD and ankylosing spondylitis –

-- Positions PAS-004 for potential expansion beyond MAPK pathway driven tumors into inflammatory diseases –

-- PAS-004 outperforms FDA-approved MEK inhibitor selumetinib in targeting ETS2 pathway –

-- Study conducted at Francis Crick Institute by lead author of 2024 Nature paper that identified ETS2 as a central regulator of macrophage-driven Inflammation in IBD--

MIAMI, May 20, 2025 (GLOBE NEWSWIRE) -- Pasithea Therapeutics Corp. (NASDAQ: KTTA) ("Pasithea" or the "Company"), a clinical-stage biotechnology company developing PAS-004, a next-generation macrocyclic MEK inhibitor, today announced new preclinical data demonstrating that PAS-004 provides superior inhibition of ETS2-driven inflammatory responses compared to selumetinib in a human macrophage model of chronic inflammation that mimics the inflammatory milieu seen in inflammatory bowel disease (IBD).

This study was conducted at the Francis Crick Institute in London, U.K. by Dr. James Lee, a gastroenterologist and Clinician Scientist Group Leader at the Genetic Mechanisms of Disease Laboratory. Dr. Lee was the lead author of a landmark 2024 *Nature* paper that identified ETS2 as a master regulator of inflammatory responses in IBD, and uncovered a novel genetic mechanism behind the disease, which pointed to a new, potentially effective treatment strategy through MEK inhibition.

In this new study RNA sequencing was used to measure gene expression, with PAS-004 consistently outperforming the FDA-approved MEK inhibitor selumetinib across all tested doses (0.01 μM, 0.1 μM, and 1 μM), showing greater downregulation of ETS2 target genes, as well as experimentally validated MEK1/2 pathway genes. These data suggest more robust and durable MEK inhibition by PAS-004 under inflammatory conditions.

Key findings of this study are:

- ***Superior and stronger suppression of ETS2 signaling.*** At all doses, PAS-004 showed greater downregulation of ETS2-regulated genes than selumetinib.

- ***Suppression of core macrophage functions***: PAS-004 significantly reduced ETS2-dependent functions such as cytokine production, phagocytosis, and reactive oxygen species (ROS) generation, all known to be central to chronic inflammation.

- ***Deeper mechanistic engagement***: Gene Set Enrichment Analysis revealed that PAS-004's effects more closely mirrored ETS2 knockout profiles, with a higher normalized enrichment score (-3.96 vs -3.56) and greater statistical significance (1.2×10^{-250} vs 3.7×10^{-74}) as compared to selumetinib.

Dr. Lee commented, "Collectively, these *in vitro* data suggest that, compared to selumetinib, PAS-004 is likely to provide superior inhibition of the macrophage inflammatory pathways orchestrated by ETS2. Blocking single cytokines is a common strategy used to treat chronic inflammatory diseases, but growing evidence suggests that targeting several at once may be a better approach. Blocking ETS2 signaling through MEK1/2 inhibition affects multiple cytokines, including TNFα and IL-23, which are individually targeted by existing therapies, and IL-1β, which has been implicated in treatment resistance and is not directly modulated by JAK inhibitors."

"JAK inhibitors have dominated the IBD oral treatment landscape over the last few years and we now have genetic evidence that MEK inhibition should affect a broader range of pathogenic cytokines including IL-1β, a critical cytokine that JAK inhibitors do not impact," commented Dr. Tiago Reis Marques, Chief Executive Officer of Pasithea. Dr. Marques continued "Based on the low level of adverse events and tolerable safety data we have observed in our Phase 1 clinical trial in advanced cancer patients, we believe PAS-004 has the potential to be a new oral treatment option for those suffering from inflammatory diseases such as IBD and we look forward to continuing to demonstrate proof-of-concept for PAS-004 in these additional indications."

Dr. Larry Steinman, Executive Chairman of Pasithea, added, "I have studied inflammation and inflammatory pathways for over 50 years and today's results are exciting as we consider better drugs targeting inflammatory conditions. These preclinical results suggest PAS-004's ability to block ETS2 signaling and target multiple cytokines opens the potential for testing PAS-004 in large market inflammatory indications."

About Pasithea Therapeutics Corp.

Pasithea is a clinical-stage biotechnology company focused on the discovery, research and development of innovative treatments for central nervous system (CNS) disorders, RASopathies and MAPK pathway driven tumors.

Forward Looking Statements

This press release contains statements that constitute "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include statements regarding the Company's ongoing Phase 1 clinical trial of PAS-004 in advanced cancer patients, the Company's Phase 1/1b clinical trial of PAS-004 in adult NF1 patients, and the safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PD) and preliminary efficacy of PAS-004, as well as all other statements, other than statements of historical fact, regarding the Company's current views and assumptions with respect to future events regarding its business, as well

as other statements with respect to the Company's plans, assumptions, expectations, beliefs and objectives, the success of the Company's current and future business strategies, product development, pre-clinical studies, clinical studies, clinical and regulatory timelines, market opportunity, competitive position, business strategies, potential growth opportunities and other statements that are predictive in nature. Forward-looking statements are subject to numerous conditions, many of which are beyond the control of the Company. While the Company believes these forward-looking statements are reasonable, undue reliance should not be placed on any such forward-looking statements, which are based on information available to the Company on the date of this release. These forward-looking statements are based upon current estimates and assumptions and are subject to various risks and uncertainties, including risks that future clinical trial results may not match results observed to date, may be negative or ambiguous, or may not reach the level of statistical significance required for regulatory approval, as well as other factors set forth in the Company's most recent Annual Report on Form 10-K, Quarterly Report on Form 10-Q and other filings made with the U.S. Securities and Exchange Commission (SEC). Thus, actual results could be materially different. The Company undertakes no obligation to update these statements whether as a result of new information, future events or otherwise, after the date of this release, except as required by law.

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