CalciMedica Announces Publication in JCI Insight of Preclinical Data Supporting CRAC Channel Inhibitor as a Potential Therapy for Pulmonary Arterial Hypertension

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Preclinical data support CRAC channel inhibitor, CM5480, as a potential first-in-class, differentiated therapy for pulmonary arterial hypertension (PAH), both as monotherapy and in combination with existing treatments

Cardiac benefit supports the mechanistic rationale for CRAC channel inhibition in acute kidney injury (AKI), being evaluated in the Phase 2 KOURAGE trial with data expected in 1H 2026

LA JOLLA, Calif., Nov. 12, 2025/PRNewswire/ -- CalciMedica Inc. ("CalciMedica" or the "Company") (Nasdaq: CALC), a clinical-stage biopharmaceutical company focused on developing novel calcium release-activated calcium (CRAC) channel inhibition therapies for acute and chronic inflammatory and immunologic illnesses, today announced a publication in *JCI* (Journal of Clinical Investigation) *Insight* of data from a preclinical study investigating one of its proprietary drug candidates, CM5480, as a potential new therapy for pulmonary arterial hypertension (PAH). CM5480 acts by selectively and potently inhibiting CRAC channels, of which Orai1 is the pore-forming subunit, to control the entry of calcium ions into cells. This mechanism is the same as CalciMedica's lead drug candidate, Auxora™, which is currently in clinical development for acute kidney injury (AKI) and acute pancreatitis.

The study, entitled, " Combination of Orai1 Inhibitor CM5480 with Specific Therapy Mitigates Pulmonary Hypertension and Its Cardiac Dysfunction ," was co-authored by Sudarshan Hebbar, M.D., CMO of CalciMedica, and Kenneth A. Stauderman, Ph.D., co-Founder and CSO of CalciMedica. Experiments were conducted by Fabrice Antigny, Ph.D., Director of Research at the French National Institute of Health and Medical Research (Inserm), within the department of Marc Humbert, M.D., Ph.D., Professor of Respiratory Medicine at Université Paris-Saclay and Head of the Pneumology Department at Bicêtre Hospital, both also co-authors of the paper and leading PAH researchers.

PAH is a rare pulmonary vascular disease characterized by progressive narrowing and thickening of pulmonary arteries, resulting in chronic elevation in pulmonary artery pressure and pulmonary vascular resistance (PVR), leading to right ventricular (RV) hypertrophy, RV dysfunction (RVD), RV failure (RVF), and eventually death. Current standard of care (SOC) therapies for patients with PAH target several key disease-related signaling pathways but do not address the Orai1 pathway. These SOC therapies are not curative and do not directly target RV function, which is the primary determinant of prognosis in PAH. It is important, therefore, to develop new treatment strategies targeting both RV function and pulmonary vascular disease. Previous preclinical studies have demonstrated that dysregulation of calcium entering pulmonary smooth muscle and endothelial cells through CRAC channels is a critical contributor to the pathogenesis of PAH and RVD. Furthermore, translational studies have found that Orai1 expression is increased in pulmonary arterial smooth muscle cells and pulmonary venous smooth muscle cells in patients with pulmonary veno-occlusive disease (PVOD), a rare form of PAH.

"Despite recent improvements in the treatment of PAH, it remains a severe disease for which there is no cure, and patients often progress to RVF," said Dr. Humbert. "We continue to search for new potential drugs with novel mechanisms that can enhance current treatment strategies. Our translational work has suggested that CRAC channel inhibition could offer such a mechanism, and the results from these in vitro and in vivo models further support this hypothesis."

In the study, investigators evaluated CM5480 as both a monotherapy and combination therapy with two SOC PAH therapies in an animal model of PAH. Pulmonary hypertension was induced in rats by monocrotaline (MCT) exposure and then CM5480 was administered daily at 20 mg/kg. Between day 14 and day 21 in the study, the rats were treated with CM5480, either alone or in combination with ambrisentan, an endothelin-1 receptor antagonist, or with sildenafil, a phosphodiesterase type 5 inhibitor.

The study found significant reductions in pulmonary neomuscularization, RV systolic pressure (RVSP), PVR, and RV hypertrophy in MCT rats treated with CM5480 as a monotherapy. RV remodeling was also reduced in CM5480-treated rats, and several pathways and functions that become dysregulated in animals with PAH were restored or improved. These included heart contraction and cardiac output, gene expression profiles impacted by the disease, DNA repair, and metabolic pathways. Dual therapies combining CM5480 with either ambrisentan or sildenafil yielded significantly greater benefits than the respective therapies administered independently, including more pronounced reductions of RVSP and RV hypertrophy, as well as more prominent improvements in PVR and pulmonary vessel and RV remodeling.

"Given PAH is a complex disease involving several dysregulated signaling pathways, the most effective treatment will likely involve a combination of drugs," said Dr. Antigny. "These preclinical results show that targeting Orai1 delivered several key benefits: it improved pulmonary vascular remodeling by reducing pulmonary arterial smooth muscle cell and pulmonary endothelial cell dysfunctions; it improved RVD; and combination therapy with CM5480 provided significantly greater benefits in reducing pulmonary arterial remodeling and improving cardiac function compared to monotherapies. This suggests Orai1 inhibition as a potential new therapeutic approach for PAH."

"Beyond PAH, these results have implications for our clinical programs, suggesting CRAC channel inhibition may directly improve the RVD seen in roughly half of patients with sepsis, the leading cause of AKI," said Dr. Hebbar of CalciMedica. "RVD in septic patients is associated with a three-fold increase in 28-day mortality. If CRAC channel inhibitors such as Auxora improve RVD, this may translate into clinical benefit for patients in our ongoing Phase 2 KOURAGE trial evaluating Auxora in severe AKI with acute hypoxemic respiratory failure."

About CalciMedica

CalciMedica is a clinical-stage biopharmaceutical company focused on developing novel CRAC channel inhibition therapies for inflammatory and immunologic diseases. CalciMedica's proprietary technology targets the inhibition of CRAC channels to modulate the immune response and protect against tissue cell injury, with the potential to provide therapeutic benefits in life-threatening inflammatory and immunologic diseases for which there are currently no approved therapies. CalciMedica's lead product candidate Auxora™ has demonstrated positive and consistent clinical results in multiple completed efficacy clinical trials and been well-tolerated in over 350 critically ill patients dosed. CalciMedica has announced data for a Phase 2b trial (called CARPO – NCT04681066) in patients with acute pancreatitis (AP) and accompanying systemic inflammatory response syndrome (SIRS) and for a Phase 2 trial (called CARDEA – NCT04345614) in patients with COVID pneumonia. The Company is currently conducting a Phase 2 trial (called KOURAGE – NCT06374797) in patients with acute kidney injury (AKI) with associated respiratory failure, with data expected in the first half of 2026. For more information, please visit www.calcimedica.com .

Forward-Looking Statements

This communication contains forward-looking statements which include, but are not limited to CalciMedica's planned and ongoing clinical trials and the timing, design, expected patient enrollment thereof and the expected timing for updates and the release of data from its Phase 2 KOURAGE trial of Auxora in AKI with associated respiratory failure in the first half of 2026; and the potential of CalciMedica's proprietary technology to provide therapeutic benefits in PAH and other acute and chronic inflammatory and immunologic diseases such as AKI and AP. These forward-looking statements are subject to the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. CalciMedica's expectations and beliefs regarding these matters may not materialize. Actual outcomes and results may differ materially from those contemplated by these forward-looking statements as a result of uncertainties, risks, and changes in circumstances, including but not limited to risks and uncertainties related to: the impact of fluctuations in global financial markets on CalciMedica's business and the actions it may take in response thereto; CalciMedica's ability to execute its plans and strategies; the ability to obtain and maintain regulatory approval for Auxora; results from clinical trials or preclinical studies may not be indicative of results that may be observed in the future; potential safety and other complications from Auxora; the scope, progress and expansion of developing and commercializing Auxora; the size and growth of the market therefor and the rate and degree of market acceptance thereof; economic, business, competitive, and/or regulatory factors affecting the business of CalciMedica generally; CalciMedica's ability to protect its intellectual property position; the impact of government laws and regulations; and CalciMedica's financial position and need for additional capital. Additional risks and uncertainties that could cause actual outcomes and results to differ materially from those contemplated by the forward-looking statements are included under the caption "Risk Factors" in CalciMedica's Quarterly Report on Form 10-Q for the quarter ended September 30, 2025, being filed with the Securities and Exchange Commission (SEC) later today, and elsewhere in CalciMedica's subsequent reports on Form 10-K, Form 10-Q or Form 8-K filed with the SEC from time to time and available at www.sec.gov . These documents can be accessed on CalciMedica's web page at ir.calcimedica.com/financials-filings/sec-filings . The forward-looking statements contained herein are made as of the date hereof, and CalciMedica undertakes no obligation to update them after this date, except as required by law.

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