Keros Therapeutics Presents Preclinical and Clinical Data from its KER-012 Program at the American Thoracic Society International Conference

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LEXINGTON, Mass., May 22, 2023 (GLOBE NEWSWIRE) -- Keros Therapeutics, Inc. (“Keros”) (Nasdaq: KROS), a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel treatments for patients suffering from hematological, pulmonary and cardiovascular disorders with high unmet medical need, today announced that it presented additional biomarker data from its completed Phase 1 clinical trial of KER-012 in healthy post-menopausal women at the American Thoracic Society (“ATS”) 2023 International Conference, held from May 19 through May 24, 2023. In addition, Keros presented preclinical data showing the potential of a research form of KER-012 (“RKER-012”) to improve left ventricular function in a mouse model of left ventricular pressure overload, as well as preclinical data evaluating transforming growth factor-beta (“TGF-β”) signaling in two major cell types involved in the dysregulated vascular remodeling in pulmonary arterial hypertension (“PAH”), and KER-012’s effect on this ligand-induced signaling.

“We are pleased to present clinical and preclinical data from our KER-012 program at the ATS conference this year. The preclinical presentations demonstrate observed ligand selectivity of KER-012 and changes in inflammation and fibrosis in models of PAH and cardiovascular diseases. From our completed Phase 1 clinical trial of KER-012 in healthy post-menopausal women, we presented new data with observed sustained changes in serum biomarkers of cardiac dysfunction, inflammation and fibrosis,” said Jasbir S. Seehra, Ph.D., President and Chief Executive Officer of Keros. “We believe these data support the potential of KER-012 to treat fibrosis and inflammation in patients with PAH and in patients with cardiovascular disease.”

Clinical Presentation

- *Administration of KER-012, a Modified Activin Receptor IIB Ligand Trap, Led to Changes in Biomarkers of Cardiovascular Health in a Ph1 Study Conducted in Healthy Post-Menopausal Women*

This Phase 1 clinical trial was a randomized, double-blind, placebo-controlled, two-part trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of KER-012. Keros reported preliminary topline data from the Part 1 single ascending dose portion of the trial in May 2022, and additional preliminary clinical data from the Part 2 multiple ascending dose portion of the trial in September 2022.

The following data from the subjects enrolled in the highest dose cohort (4.5 mg/kg) from Part 2 of this trial were presented at ATS 2023:

- Serum proteins associated with inflammation and structural remodeling pathways were altered following one dose of 4.5 mg/kg of KER-012 versus placebo, which Keros believes is consistent with the predicted mechanism of action of KER-012:
  - Decreases in markers of fibrosis, as indicated by changes in matrix metalloproteinases (MMP-7 and 10) and collagen fragments, were observed;
  - Reductions in pro-inflammatory cytokines (IL-6 and IL-11) were observed; and
  - Increases in anti-inflammatory cytokines (IL-4 and IL-35) and markers of macrophage polarization (MARCO and sCD163) were also observed.
- Sustained reductions in a biomarker of cardiac dysfunction (serum N-terminal pro-brain natriuretic peptide) were observed in subjects administered 4.5 mg/kg of KER-012 versus placebo.

Preclinical Presentations

- *RKER-012, a Novel Modified ActRII Ligand Trap, Attenuated Cardiac Remodeling and Fibrosis in a Transverse Aortic Constriction Model of Heart Failure*

Keros used a transverse aortic constriction (“TAC”) model of left ventricle overload to evaluate whether RKER-012 could prevent or treat cardiac remodeling and fibrosis in mice.

Mice either underwent sham or TAC surgery. Following these procedures, sham mice received vehicle and TAC mice received either vehicle (“TAC-vehicle”) or 10 mg/kg of RKER-012 (“TAC-RKER-012”) twice weekly, starting from the first day (“TAC-RKER-012 Group 1”) or fourteenth day (“TAC-RKER-012 Group 2”) after surgery. Eight weeks post-surgery, mice were assessed for associated cardiac pathologies. Relative to sham mice, TAC-vehicle mice had increased heart weight, left ventricular posterior wall thickness, interventricular septal end diastole, left ventricular fibrosis and elevated tissue remodeling markers, indicating that the TAC surgery worked as intended.

TAC-RKER-012 Group 1 mice had significantly reduced heart weight, left ventricular posterior wall thickness, interventricular septal end diastole and

left ventricular fibrosis compared to TAC-vehicle mice. TAC-RKER-012 Group 2 mice had significantly reduced left ventricular posterior wall thickness and interventricular septal end diastole compared to TAC-vehicle mice, while heart weight and left ventricular fibrosis trended towards a decrease.

These data demonstrate that RKER-012 lessened the severity of cardiac fibrosis and remodeling, leading to an improvement in left ventricular function, which Keros believes supports the potential of KER-012 to benefit heart failure patients as a preventative or treatment option.

- *RKER-012, a Novel Activin Receptor Type IIB (ActRIIB) Ligand Trap, Inhibited Mediators of Dysregulated Vascular Remodeling in Pulmonary Endothelial and Smooth Muscle Cells*

This preclinical study evaluated TGF-β ligand signaling in human pulmonary arterial endothelial cells (“HPAECs”) and smooth muscle cells (“HPASMCs”), which are two major cell types involved in the dysregulated vascular remodeling in PAH, and KER-012’s effect on this ligand-induced signaling.

HPAECs and HPASMCs were treated with activin A, GDF11, or bone morphogenetic protein 9 (“BMP9”) in the presence of KER-012. KER-012 treatment reduced activin A and GDF11-induced SMAD 2/3 signaling in the HPAECs and HPASMCs, but did not inhibit BMP9-induced pSMAD1 signaling.

Separately, pulmonary arterial cells cultured in normoxia or hypoxia for 48 hours to mimic conditions in PAH were evaluated with RKER-012. Keros observed increases in activin A induced by hypoxia in HPAECs, but not in HPASMCs, which is consistent with the role of endothelial dysfunction in PAH and suggests that activin A may be released from endothelial cells during vascular remodeling. RKER-012 was able to reduce SMAD2 activation in hypoxic endothelial cells back to normoxic levels by binding endogenously upregulated activin A in an in vitro model replicating hypoxia in PAH.

These data from this in vitro model suggest that KER-012 can potentially correct imbalanced SMAD signaling in PAH, partially by inhibiting activin A, a key pathogenic driver of PAH.

About the Completed Phase 1 Clinical Trial of KER-012 in Healthy Volunteers

In September 2022, Keros completed a randomized, double-blind, placebo-controlled, two-part Phase 1 clinical trial to evaluate single and multiple ascending doses of KER-012 in healthy post-menopausal women. The primary objectives of this trial were to evaluate the safety and tolerability of escalating doses of KER-012 administered as single and multiple subcutaneous doses in healthy post-menopausal women.

In Part 1 of this trial, 32 subjects received either a single 0.75, 1.5, 3 or 5 mg/kg dose of KER-012 and eight subjects received a single dose of placebo, each administered subcutaneously with an eight-week safety follow-up. The subjects were enrolled in sequential single-ascending dose escalation cohorts of ten subjects each. In Part 2 of the trial, subjects received three subcutaneous doses of either 0.75, 1.5 or 4.5 mg/kg of KER-012 or placebo administered 28 days apart with a 16-week safety follow-up. A total of 26 subjects were enrolled in three sequential multiple-ascending dose escalation cohorts, with eight subjects in the 0.75 mg/kg cohort and six subjects in each of the 1.5 mg/kg and 4.5 mg/kg cohorts receiving KER-012. Six subjects enrolled in Part 2 of this trial received placebo doses.

About KER-012

KER-012 is designed to bind to and inhibit the signaling of TGF-β ligands that suppress bone growth, including activin A and activin B. Keros believes that KER-012 has the potential to increase the signaling of bone morphogenic protein (“BMP”) pathways through this inhibition of activin A and activin B signaling, and consequently treat diseases such as PAH that are associated with reduced BMP signaling due to inactivating mutations in the BMP receptors. KER-012 is being developed for the treatment of PAH and for the treatment of cardiovascular disorders.

About Keros Therapeutics, Inc.

Keros is a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel treatments for patients suffering from hematological, pulmonary and cardiovascular disorders with high unmet medical need. Keros is a leader in understanding the role of the TGF-β family of proteins, which are master regulators of red blood cell and platelet production as well as of the growth, repair and maintenance of a number of tissues, including blood vessels and heart tissue. Keros’ lead protein therapeutic product candidate, KER-050, is being developed for the treatment of low blood cell counts, or cytopenias, including anemia and thrombocytopenia, in patients with myelodysplastic syndromes and in patients with myelofibrosis. Keros’ lead small molecule product candidate, KER-047, is being developed for the treatment of functional iron deficiency. Keros’ third product candidate, KER-012, is being developed for the treatment of PAH and for the treatment of cardiovascular disorders.

Cautionary Note Regarding Forward-Looking Statements

Statements contained in this press release regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Words such as "believes," "intends," “potential” and "suggest" or similar expressions are intended to identify forward-looking statements. Examples of these forward-looking statements include statements concerning: Keros’ expectations regarding its growth, strategy, progress and the design, objectives and timing of its clinical trials for KER-012; the potential of KER-012 to treat fibrosis and inflammation in patients with PAH and in patients with cardiovascular disease; the potential of KER-012 to benefit heart failure patients as a preventative or treatment option; and the potential of KER-012 to correct imbalanced SMAD signaling in PAH. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. These risks and uncertainties include, among others: Keros’ limited operating history and historical losses; Keros’ ability to raise additional funding to complete the development and any commercialization of its product candidates; Keros’ dependence on the success of its product candidates, KER-050, KER-047 and KER-012; that Keros may be delayed in initiating, enrolling or completing any clinical trials; competition from third parties that are developing products for similar uses; Keros’ ability to obtain, maintain and protect its intellectual property; and Keros’ dependence on third parties in connection with manufacturing, clinical trials and preclinical studies.

These and other risks are described more fully in Keros’ filings with the Securities and Exchange Commission (“SEC”), including the “Risk Factors” section of the Company’s Quarterly Report on Form 10-Q, filed with the SEC on May 4, 2023, and its other documents subsequently filed with or furnished to the SEC. All forward-looking statements contained in this press release speak only as of the date on which they were made. Except to the extent required by law, Keros undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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