Keros Therapeutics Presents Preclinical Data from ALK2 and KER-050 Hematology Programs at the European Hematology Association EHA2021 Virtual Congress

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- *Multiple poster presentations demonstrate that ALK2 inhibition lowered hepcidin levels and improved iron homeostasis in preclinical models of anemia and iron overload.*
- *Poster presentation demonstrates that KER-050 had effects on multiple stages of erythroblast maturation (both early- and late-stage) and increased circulating erythropoietin in preclinical models. The observed rapid and durable effects on erythropoiesis provide continued support for KER-050 as a potential treatment for ineffective hematopoiesis in myelodysplastic syndromes ("MDS") and myelofibrosis.*

LEXINGTON, Mass., June 11, 2021 (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 and musculoskeletal disorders with high unmet medical need, today presented data from the ALK2 and KER-050 hematology programs at the European Hematology Association EHA2021 Virtual Congress held from June 9 through June 17, 2021.

"We are pleased to be able to present multiple posters at this year's EHA2021 Virtual Congress. Our preclinical studies continue to elucidate the relationship between ALK2 inhibition, hepcidin and serum iron. These data support that ALK2 inhibition may be a potential treatment option for indications associated with high hepcidin, including anemia of inflammation ("AI") and iron refractory iron-deficiency anemia ("IRIDA"). In addition, the data suggests that ALK2 inhibition has the potential to mobilize and reduce tissue iron in diseases of iron overload," said Jasbir S. Seehra, Ph.D., Chief Executive Officer of Keros. "We also presented new preclinical data for KER-050 that demonstrated its rapid and durable effects on erythropoiesis and increases in circulating erythropoietin, which we believe provides a strong rationale for investigating KER-050 as a treatment for ineffective hematopoiesis in MDS and myelofibrosis."

Details of the presentations are as follows:

Inhibition of ALK2 Through Administration of a Small Molecule Inhibitor Decreased Hepcidin, Increased Serum Iron and Ameliorated Anemia in an Induced Model of Anemia of Inflammation

- *ALK2 is a potential therapeutic target in anemia resulting from chronic inflammation* **-** *Abstract Number*: EP839

To induce a model of chronic kidney disease ("CKD"), mice were dosed daily for six weeks with 50 mg/kg of adenine, leading to iron deficiency anemia (37.6% decrease in serum iron; $p<0.0001$), associated with increased circulating interleukin-6 ("IL6") (2.42-fold; $p<0.05$) and hepcidin (3.49-fold; $p<0.01$). After completing the six weeks of adenine-administration, we administered 5 mg/kg of either a selective small molecule ALK2 kinase inhibitor ("KTI-2338"), or vehicle daily for 10 days in the CKD mice, and observed a reversal of the CKD-related changes in the KTI-2338-treated mice. We observed an increase in serum iron (108.2%; $p<0.0001$), decrease in hepcidin (85.4%; $p<0.0001$) and improvements in red blood cell ("RBC") count (7.2%; ns), hemoglobin ("HGB") (10.9%; $p<0.0001$) and hematocrit (10.3%; $p<0.05$) compared to vehicle. Reticulocyte hemoglobin ("RET-HGB") content, a measure of the incorporation of iron into hemoglobin, increased 9.9% ($p<0.01$) with KTI-2338 compared to vehicle-treated CKD mice, normalizing to baseline levels.

These data demonstrate that inhibition of ALK2 improved hematological markers of anemia, serum hepcidin and serum iron levels in a mouse model of AI resulting from chronic kidney disease characterized by elevated IL6, suggesting that targeting ALK2 inhibition could potentially treat anemia arising from high hepcidin.

Administration of an ALK2 Inhibitor in a Mouse Model of Iron Overload Resulted in Significant Reductions in Liver Non-Heme Iron

- *ALK2 inhibition, a novel therapeutic approach to iron overload* **-** *Abstract Number*: EP842

Administration of KTI-2338 reduced circulating hepcidin levels and increased serum iron in wild-type mice after three days of daily dosing. Specifically, we observed a reduction in hepcidin as soon as four hours post the third administration of KTI-2338, which was sustained through 12 hours post-administration, as well as an increase in serum iron eight hours post-administration, which peaked at 16 hours post-administration.

Mice were dosed daily with 100 mg/kg of iron dextran to induce iron overload and subsequently dosed with either KTI-2338 (5 mg/kg) or vehicle. Mice dosed with iron dextran became iron overloaded and exhibited a substantial 47-fold increase in hepatic iron compared to mice that received vehicle ($p<0.0001$). Our initial results indicated that, after 63 hours of dosing with KTI-2338, there were significant reductions in liver non-heme iron content (62%). Subsequent analysis using a more selective iron assay confirmed that treatment with KTI-2338 reduced non-heme iron (13.4%) compared to vehicle treated mice ($p<0.006$).

These data suggest that, in conditions with iron overload, ALK2 inhibition may potentially be used to remove excess iron from the liver, potentially improving the effectiveness of chelation therapy and excretion.

Treatment with ALK2 Antibodies to Neutralize the ALK2 Receptor Reduced Serum Hepcidin and Increased Circulating Iron in Non-Human Primates, a Preclinical Model Highly Representative of Human Biology

- *Administration of ALK2 neutralizing antibodies to cynomolgus monkeys led to a sustained decrease in hepcidin, increase in circulating iron and increase in erythrocyte hemoglobin - Abstract Number*: EP840

Keros has developed two fully human antibodies, KTI-016 and KTI-018, that are designed to specifically bind to and neutralize the ALK2 receptor. To determine the pharmacokinetic and pharmacodynamic properties of these antibodies, female cynomolgus monkeys received a single subcutaneous dose (3 mg/kg) of either antibody. Serum drug concentrations and indices of iron and hematology were assessed intermittently over an 8-week period. KTI-016 and KTI-018 were both rapidly absorbed, reached C_{max} within 48 hours and had half-lives of 49.1 hours and 33.9 hours, respectively.

Six hours after administration, KTI-016 and KTI-018 reduced serum hepcidin by 50.3% and 55.6%, respectively. The reduction in hepcidin peaked starting at 48 hours post-administration, at 77.8% in the KTI-016-treated group and 77.2% in the KTI-018-treated group. These decreases remained through day 10 before returning to baseline by day 14. A corresponding increase in circulating iron occurred starting at 24 hours following administration, peaking at 63.9% ($p<0.01$) and 72.4% ($p<0.001$) in the KTI-016- and KTI-018-treated groups, respectively. This response was also sustained through day 10, returning to baseline by day 14.

KTI-016 and KTI-018 were also observed to have comparable effects on increasing RET-HGB, red blood cell hemoglobin (“RBC-HGB”) and mean corpuscular hemoglobin concentration (“MCHC”) (data from the two antibodies were combined). RET-HGB increased by 4.9% ($p<0.001$) at 3 days post-dose and remained elevated for at least 10 days. Increases in RBC-HGB content were observed initially at 35 days post-dose, with a 4.2% increase ($p<0.0001$) at day 56. We also observed increases in MCHC starting at 42 days post-dose, with a 3.7% increase ($p<0.001$) at day 56.

We believe iron mobilized by treatment with KTI-016 and KTI-018 was incorporated into hemoglobin, as evidenced by the observed increases in RET-HGB, RBC-HGB and MCHC. Accordingly, these data demonstrate that these antibodies may be a potential treatment for anemias arising from elevated hepcidin, such as IRIDA and AI.

Preclinical Study of KER-050 Demonstrated Effects on Multiple Stages of Erythroblast Maturation and Increased Circulating Erythropoietin

- *KER-050, an inhibitor of TGF-β superfamily signaling, observed to have a rapid, dynamic, and durable effect on erythropoiesis - Abstract Number*: EP758

Mice treated with a single dose of a research form of KER-050 (“RKER-050”) showed rapid and sustained increases in RBCs and HGB, observed from 12 hours (RBCs +8%; $p<0.001$ and HGB +9%; $p<0.005$) through day 51 (RBCs + 8% $p<0.001$), compared to vehicle-treated mice.

Treatment with RKER-050 also resulted in a dynamic mobilization of erythroblasts from the bone marrow into circulation. At 12 hours post-administration, we observed a 20% reduction in bone marrow (“BM”) proerythroblasts that corresponded to a 37% increase in erythroblasts at 24 hours post-administration, which we believe indicates that early progenitors were differentiating into erythroblasts. We also observed an increase in mature erythroblasts, which suggests the differentiation of late-stage progenitors. This maturation of erythroblasts corresponded to an increase in circulating reticulocytes (“RETs”) at 12 hours post-administration (+18%; $p<0.05$), as well as to an increase in RBCs observed at 48 hours post-dose (+8% $p<0.0001$).

The initial increase in RETs observed at 12 hours post-administration was reduced (-15%; $p<0.05$) at 24 hours post-administration, which we believe indicates that RETs matured to RBCs. At 48 hours post-administration, RET numbers returned to vehicle-comparable levels, which we believe indicates that the RET pool was replenished. This data potentially demonstrates that there was a continued progression of erythroblasts through maturation. This increased differentiation and maturation of erythroblast contributed to a sustained upregulation of erythropoiesis at day 14 post-dose.

In the RKER-050-treated mice, erythropoietin upregulation was not observed until day 4. However, erythropoietin was significantly increased from day 7 (+68%, $p<0.0001$) through day 37 (4-fold increase, $p<0.05$) which potentially indicates that erythropoietin has a contributing role in sustaining the RKER-050-mediated increase in RBCs and HGB, compared to vehicle, through at least day 51.

We believe the observed rapid and durable effect on erythropoiesis via multiple stages of erythroblast maturation (both early- and late-stage) as well as the observed increase in circulating erythropoietin provides a strong rationale for investigating KER-050 as a potential treatment for ineffective erythropoiesis in MDS and myelofibrosis.

About KER-050

Keros’ lead protein therapeutic product candidate, KER-050, is an engineered ligand trap comprised of a modified ligand-binding domain of the Transforming Growth Factor-Beta receptor known as activin receptor type IIA that is fused to the portion of the human antibody known as the Fc domain. KER-050 is being developed for the treatment of low blood cell counts, or cytopenias, including anemia and thrombocytopenia, in patients with myelodysplastic syndromes, or MDS, and in patients with myelofibrosis. In October 2020, Keros announced the dosing of the first two participants in its Phase 2 clinical trial evaluating KER-050 for the treatment of anemia and thrombocytopenia in very low-, low-, or intermediate-risk MDS. Keros expects to report initial data from Part 1 of this trial by the end of June 2021. Additionally, Keros plans to commence an open-label Phase 2 clinical trial evaluating KER-050 for the treatment of patients with myelofibrosis-associated cytopenias in the third quarter of 2021 and expects to report initial data from this trial in 2022.

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 hematologic and musculoskeletal disorders with high unmet medical need. Keros is a leader in understanding the role of the Transforming Growth Factor-Beta family of proteins, which are master regulators of red blood cell and platelet production as well as of the growth, repair and maintenance of muscle and bone. 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 anemia resulting from iron imbalance, as well as for the treatment of fibrodysplasia ossificans progressiva. Keros’ third product candidate, KER-012, is being developed for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of pulmonary arterial hypertension.

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 "anticipates," "believes," "expects," "intends," “plans,” “potential,” "projects,” “would” and "future" 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 timing of its clinical trials for KER-050; the potential of KER-050 to treat diseases that exhibit defects in different stages of erythropoiesis, including MDS and myelofibrosis; the potential of ALK2 inhibition to treat a variety of indications, including iron overload and anemias that arise from elevated hepcidin, such as IRIDA and AI; and the potential of ALK2 inhibition to improve the effectiveness of chelation therapy and excretion. 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 lead product candidates, KER-050 and KER-047; 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; Keros’ dependence on third parties in connection with manufacturing, clinical trials and pre-clinical studies; and risks relating to the impact on our business of the COVID-19 pandemic or similar public health crises.

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 6, 2021, 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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