Kymera Therapeutics Announces Positive Interim Results from Single Ascending Dose Phase 1 Trial of KT-474 Demonstrating Degrader Proof-of-Mechanism

June 28, 2021

KT-474 has achieved and exceeded Phase 1 target degradation of 85% within the SAD portion of the Phase 1 trial dosed to date, with 90% median degradation at the 300 mg dose

After single dose administration, degradation was maintained for at least six days at all dose levels, with no treatment-related adverse events observed to date

Data represent the first proof-of-mechanism for targeted protein degradation in a randomized, placebo-controlled healthy volunteer study

FDA has lifted partial clinical hold on Multiple Ascending Dose portion of Phase 1 trial and Kymera plans to initiate repeat dosing in July 2021

Kymera to host conference call today at 8 a.m. ET

WATERTOWN, Mass., June 28, 2021 (GLOBE NEWSWIRE) -- Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing targeted protein degradation to deliver novel small molecule protein degrader medicines, today announced positive interim results from the Single Ascending Dose (SAD) portion of the Phase 1 clinical trial of KT-474, demonstrating the first degrader proof-of-mechanism in targeted protein degradation in a randomized, placebo-controlled healthy volunteer study. KT-474 has achieved and exceeded the Phase 1 target degradation of 85% within the SAD portion of the Phase 1 trial dosed to date, with profound IRAK4 degradation after a single oral dose that lasted for at least six days at all dose levels. The partial clinical hold on the Multiple Ascending Dose (MAD) portion of the Phase 1 trial of KT-474 has been lifted following review by the U.S. Food and Drug Administration (FDA) of interim safety, pharmacokinetic and pharmacodynamic data from the first three cohorts of the SAD healthy volunteer portion of the Phase 1 study.

In the SAD portion of the trial, healthy volunteer subjects are randomized 6:2 to either a single oral dose of KT-474 or placebo. Interim data (n=32), which also include results from the fourth cohort of the trial, showed dose and time-dependent IRAK4 degradation following single oral KT-474 dose administration (KT-474 dose levels of 25, 75, 150 and 300 mg). IRAK4 levels were measured in peripheral blood mononuclear cells (PBMC) using mass spectrometry. Following a single KT-474 oral dose, IRAK4 reduction was observed as early as eight hours post-dose, reached maximal reduction at 48 to 72 hours, and was sustained for at least six days with subsequent recovery towards pre-treatment baseline across all dose groups. In the fourth cohort, following a single 300 mg dose of KT-474, median IRAK4 reduction from baseline at 48 hours was 90% compared to a 16% increase in the placebo group ($p<0.0001$), with maximum IRAK4 reduction of 94%, demonstrating proof-of-mechanism for KT-474 (see table below). KT-474, to date, has demonstrated oral bioavailability, predictable and dose-dependent plasma exposures, and a half-life supportive of oral daily dosing. No treatment-related adverse events have been observed to date.

“This study marks the first time a heterobifunctional small molecule degrader has been studied in humans in a placebo-controlled study,” said Nello Mainolfi, PhD, Co-Founder, President and CEO, Kymera Therapeutics. “We have shown that KT-474 can lead to rapid, marked and sustained IRAK4 reduction after a single dose. The ability to reach and sustain biologically relevant levels of target degradation after just a single dose not only validates Kymera’s platform, but importantly, further de-risks the development of KT-474 as a potentially best-in-class anti-inflammatory oral agent.”

Table: Percent IRAK4 Change from Baseline in PBMC at 48 Hours Post-Dose using Mass Spectrometry

	Placebo (n=8)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)
KT-474 dose	**-**	**25 mg**	**75 mg**	**150 mg**	**300 mg**
Median IRAK4 Change	**+16%**	**-41%** (p=0.0057)	**-71%** (p<0.0001)	**-78%** (p<0.0001)	**-90%** (p<0.0001)

KT-474 is a highly active and selective, orally bioavailable IRAK4 degrader being developed for the treatment of toll-like receptor (TLR)/interleukin-1 receptor (IL-1R)-driven immune-inflammatory diseases, such as atopic dermatitis, hidradenitis suppurativa, rheumatoid arthritis and potentially other indications. The Phase 1 clinical trial is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of KT-474 in up to 116 healthy volunteers, and in a subsequent cohort of up to 20 patients with atopic dermatitis and hidradenitis suppurativa.

“We are encouraged by the safety, pharmacokinetic and pharmacodynamic profile observed to date with single oral doses of KT-474 and look forward to initiating the MAD portion of the trial while continuing to dose escalate in the SAD portion. The IRAK4 reduction in PBMC observed after single doses of KT-474 shows robust translation of the pharmacodynamic effect from preclinical studies to humans. We are excited to have reached and exceeded our target degradation of 85% after just a single dose, and with 14 days of dosing in the MAD portion we anticipate reaching our target degradation with even lower daily doses of KT-474,” said Jared Gollob, MD, Chief Medical Officer at Kymera Therapeutics.

Kymera plans to continue dose escalation in the SAD portion of the Phase 1 trial and also assess for any food effect. In parallel, starting next month, Kymera plans to initiate repeat daily dosing of KT-474 for 14 days, beginning with the 25 mg dose, in healthy volunteers randomized 9:3 to KT-474 or placebo in the MAD portion of the trial. Kymera expects to present updated results from the healthy volunteer SAD and MAD portions of the trial in Q4’21, including IRAK4 degradation in both skin and PBMC and effects on inflammatory biomarkers. The dose level in the MAD healthy volunteer portion which demonstrates maximal IRAK4 degradation in PBMC and skin and has been well tolerated, will then be selected for evaluation in an open-label cohort of patients with atopic dermatitis and hidradenitis suppurativa (up to 20 patients). Additional information on this clinical trial can be found on www.clinicaltrials.gov.

Conference Call Information

Kymera will host a conference call and webcast today, Monday, June 28, at 8:00 a.m. ET to discuss the KT-474 program updates. To access the

conference call via phone, please dial 833-740-0921 (U.S.) or +1 409-937-8885 (International) and using the conference ID 7376053. A live webcast of the event will be available under "Events and Presentations" in the Investors section of the Company's website at www.kymeratx.com. A replay of the webcast will be archived and available for one month following the event.

About IRAK4 and KT-474

IRAK4 is a key protein involved in inflammation mediated by the activation of toll-like receptors (TLRs) and IL-1 receptors (IL-1Rs). Aberrant activation of these pathways is the underlying cause of multiple immune-inflammatory conditions. KT-474, a potential first-in-class, orally bioavailable IRAK4 degrader, is being developed for the treatment of TLR/IL-1R-driven immune-inflammatory diseases with high unmet medical need, such as atopic dermatitis, hidradenitis suppurativa, rheumatoid arthritis, and potentially others. KT-474 is designed to block TLR/IL-1R-mediated inflammation more broadly compared to monoclonal antibodies targeting single cytokines, and to enable pathway inhibition that is superior to IRAK4 kinase inhibitors by abolishing both the kinase and scaffolding functions of IRAK4. In February 2021, Kymera initiated dosing of healthy volunteers in the Single Ascending Dose portion of a first-in-human Phase 1 Single and Multiple Ascending Dose trial designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered KT-474 in adult healthy volunteers and patients with atopic dermatitis and hidradenitis suppurativa.

Kymera is collaborating with Sanofi on the development of degrader candidates targeting IRAK4, including KT-474 (SAR444656), outside of the oncology and immuno-oncology fields.

About Pegasus™

Pegasus™ is Kymera Therapeutics' proprietary protein degradation platform, created by its team of experienced drug hunters to improve the effectiveness of targeted protein degradation and generate a pipeline of novel therapeutics for previously undruggable diseases. The platform consists of informatics-driven target identification, novel E3 ligases, proprietary ternary complex predictive modeling capabilities, and degradation tools.

About Kymera Therapeutics

Kymera Therapeutics (Nasdaq: KYMR) is a clinical-stage biopharmaceutical company founded with the mission to discover, develop, and commercialize transformative therapies while leading the evolution of targeted protein degradation, a transformative new approach to address previously intractable disease targets. Kymera's Pegasus™ platform enables the discovery of novel small molecule degraders designed to harness the body's natural protein recycling machinery to degrade disease-causing proteins, with a focus on undrugged nodes in validated pathways currently inaccessible with conventional therapeutics. Kymera's initial programs are IRAK4, IRAKIMiD, and STAT3, each of which addresses high impact targets within the IL-1R/TLR or JAK/STAT pathways, providing the opportunity to treat a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors. Kymera's goal is to be a fully integrated biopharmaceutical company at the forefront of this new class of protein degrader medicines, with a pipeline of novel degrader medicines targeting disease-causing proteins that were previously intractable.

Founded in 2016, Kymera is headquartered in Watertown, Mass. Kymera has been named a "Fierce 15" biotechnology company by FierceBiotech and has been recognized by the Boston Business Journal as one of Boston's "Best Places to Work." For more information about our people, science, and pipeline, please visit www.kymeratx.com or follow us on Twitter or LinkedIn.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding its: plans to present updated results from the healthy volunteer SAD and MAD portions of the KT-474 trial; its views on KT-474 as validating its platform and approach to drug development; strategy, business plans and objectives for the IRAK4 degrader program; and plans and timelines for the clinical development of Kymera Therapeutics' product candidates, including the therapeutic potential and clinical benefits thereof. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of COVID-19 on countries or regions in which Kymera Therapeutics has operations or does business, as well as on the timing and anticipated results of its current preclinical studies and future clinical trials, strategy and future operations; the delay of any current preclinical studies or future clinical trials or the development of Kymera Therapeutics' drug candidates; the risk that topline or interim results of current clinical studies may not be predictive of future results in connection with current or future clinical trials; Kymera Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of planned interactions with regulatory authorities, including for the advancement in development of KT-474; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Quarterly Report on Form 10-Q for the period ended March 31, 2021, filed on May 6, 2021, as well as discussions of potential risks, uncertainties, and other important factors in Kymera Therapeutics' subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Kymera Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Kymera Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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