Centessa Pharmaceuticals Initiates Global Phase 3 ACTION Study of Lixivaptan in Autosomal Dominant Polycystic Kidney Disease, Reports Initial Positive Safety Data from ALERT Study, and Announces Notice of Allowance for Key Lixivaptan U.S. Patent Application

December 14, 2021

~ Initiation of registrational Phase 3 ACTION clinical study with lixivaptan is an important milestone to bring this potential new treatment option to ADPKD patients ~

~ All four subjects in the ALERT Study who previously discontinued JYNARQUE® due to liver toxicity successfully titrated to maintenance dose of lixivaptan; no subjects met pre-specified stopping criteria; no cases of suspected drug-induced liver injury (DILI) ~

~ Issuance of new patent would cover use of lixivaptan in ADPKD through at least 2038 ~

BOSTON and LONDON, Dec. 14, 2021 (GLOBE NEWSWIRE) -- Centessa Pharmaceuticals plc ("Company") (Nasdaq: CNTA), together with subsidiary Palladio Biosciences, Inc. ("Palladio"), today announced the initiation of active recruitment of the global ACTION Study, a pivotal Phase 3 clinical trial evaluating lixivaptan as a potential treatment for Autosomal Dominant Polycystic Kidney Disease (ADPKD). Additionally, the Company reported initial safety data from four subjects who participated in the ongoing open-label ALERT Study of ADPKD subjects who previously discontinued JYNARQUE® (tolvaptan) due to liver toxicity and announced the Notice of Allowance for a U.S. Patent application covering use of lixivaptan in ADPKD.

"Patients with ADPKD need alternative treatment options to the currently approved therapy, which is associated with a Risk Evaluation and Mitigation Strategies (REMS) program due to its side effect profile. I have been encouraged by the pharmacodynamic and tolerability data generated to date with lixivaptan and look forward to seeing the benefit and safety data from the upcoming pivotal ACTION Study," said Vicente Torres, MD, PhD, Professor of Medicine, Mayo Clinic and Chairman of the Steering Committee and Principal Investigator of the ACTION Study.

"We are thrilled to begin the registrational ACTION Study so we can further evaluate lixivaptan's potential as a new treatment option in the broader ADPKD patient population," said Saurabh Saha, MD, PhD, Chief Executive Officer of Centessa. "Furthermore, the initial safety data from the ALERT Study in subjects who have stopped JYNARQUE due to liver toxicity continues to support the differentiated safety and tolerability profile of lixivaptan. In addition, the allowed claims addressed in the recently issued Notice of Allowance from the U.S. Patent & Trademark Office should provide patent protection for the covered use of lixivaptan in ADPKD treatment in the U.S. to at least 2038."

"The initial safety data we shared today from the ALERT Study is similar to the case study we previously reported from the Mayo Clinic and provides additional evidence of lixivaptan's tolerability profile, especially in a group of ADPKD subjects who had previous liver chemistry abnormalities while taking tolvaptan," said Neil Shusterman, MD, Chief Medical Officer of Palladio. "We look forward to bringing this potential new treatment option to ADPKD patients."

ACTION Study Initiation

Recruitment has commenced in the global Phase 3 ACTION Study which consists of a two-arm, double-blind, placebo-controlled, randomized phase (Part 1) followed by a single-arm, open-label phase (Part 2). The study will evaluate the benefit and safety of lixivaptan that has been titrated to a maximum tolerated dose between 100-200 mg BID in subjects with ADPKD and a Mayo Clinic MRI imaging classification of 1C, 1D or 1E and an estimated glomerular filtration rate (eGFR) ≥25 and ≤90 mL/min/1.73 m^2.

The primary analysis of the ACTION Study will be performed at the end of Part 1 of the trial, which will have a 2:1 randomization (lixivaptan:placebo) and is designed to assess lixivaptan in slowing the decline in renal function as measured at 52 weeks by the difference in eGFR between the lixivaptan-treated and placebo-treated subjects. Final efficacy measurements at the end of the double-blind period will be conducted while the subject is off study drug over three successive clinic visits. The sample size of the study will be up to 1,350 subjects to provide 90% power to the primary analysis, aiming to detect a 1.4 mL/min/1.73 m^2 eGFR difference between lixivaptan-treated and placebo-treated subjects. Thirteen clinical sites have been initiated and the trial is ultimately expected to enroll subjects across more than 200 sites in more than 20 countries. As previously disclosed, the Company expects to dose the first subject in the ACTION Study by the first quarter of 2022.

All subjects successfully completing Part 1 are expected to continue into Part 2 of the study and will be treated with lixivaptan for an additional 54-56 weeks to further assess the sustainability of the potential benefit on eGFR change over a two-year period. Consistent with Part 1, updated efficacy measurements will be conducted off study drug. Both parts of the study will contribute to further establishing the safety profile of lixivaptan. An independent data monitoring committee will periodically review all safety data including the liver chemistry data for all subjects throughout the study. The Company anticipates completing enrollment in 2H 2023 and, pending positive data, plans to submit a New Drug Application (NDA) after completion of the one-year double-blind portion of the study (Part 1).

ALERT Study Update

The Company also reported initial safety data from the ongoing open-label ALERT Study of ADPKD subjects who previously discontinued JYNARQUE® (tolvaptan) due to liver toxicity. The ALERT Study is designed to assess liver and non-liver safety in subjects who previously experienced liver chemistry test abnormalities that met the criteria for likely drug-induced liver injury (DILI) while being treated with tolvaptan and who permanently discontinued the drug. Subjects in the ALERT Study undergo up to 8 weeks of screening followed by a three-week baseline measurement period and then a three- to six-week titration phase with lixivaptan, with weekly liver chemistry test monitoring during the baseline and titration phases. During the maintenance phase, liver chemistry tests are obtained every four weeks. The primary outcome measure in the study is the proportion of subjects who develop alanine aminotransferase (ALT) levels >3x ULN adjudicated to be related to lixivaptan resulting in discontinuation of the study drug.

To date, ten subjects have entered screening, five failed screening, and one failed the baseline measurement period. The four subjects who enrolled in the study had cases of DILI while being treated with tolvaptan for ADPKD and had ALT elevations that peaked between 1.8x and 3.5x ULN and did not return to below ULN until 23 to 140 days after tolvaptan use was discontinued. Each of these subjects was successfully titrated to a maintenance dose of lixivaptan of either 100 mg BID (one subject) or 200 mg BID (three subjects) and entered the maintenance phase of the study.

As of the most recent data cutoff (December 3, 2021), three out of four subjects remain on lixivaptan with the longest treatment duration being 366 days, and the remaining subjects at 174 days and 172 days on treatment. One subject successfully titrated to 200 mg BID lixivaptan but withdrew consent after 93 days of dosing. No subjects have had clinically meaningful ALT elevations attributed to lixivaptan and no subjects met the pre-specified stopping criteria of an ALT level >3x ULN.

The ALERT Study remains open for enrollment of subjects who have had a confirmed case of DILI while being treated with tolvaptan. Most subjects who stop treatment with tolvaptan due to liver toxicity are also eligible for enrollment in the ACTION Study, which is now the primary focus of the Company's recruitment efforts.

Notice of Allowance for Key Lixivaptan U.S. Patent Application

On December 3, 2021, the U.S. Patent and Trademark Office issued a Notice of Allowance for Palladio's patent application entitled "Formulations of Lixivaptan for the Treatment of Polycystic Disease," which has claims drawn to using a divided dose regimen of lixivaptan in treating ADPKD. The anticipated patent term would expire June 8, 2038, before consideration of any applicable patent term extensions or adjustments.

About Centessa Pharmaceuticals
Centessa Pharmaceuticals plc ("Centessa") aims to bring impactful new medicines to patients by combining the strengths of an asset-centric model with the benefits of scale and diversification typical of larger R&D organizations. The asset-centric model refers to a highly specialized, singular-focused company that is led by a team of well-recognized subject matter experts. Centessa's asset-centric companies' programs range from discovery-stage to late-stage development and include diverse therapeutic areas such as oncology, hematology, immunology/inflammation, neuroscience, hepatology, pulmonology and nephrology. For more information, visit www.centessa.com.

About Palladio Biosciences
Palladio Biosciences, Inc. ("Palladio") was created with the goal of developing transformative medicines for rare diseases of the kidney. Palladio is actively investigating the potential of its lead product candidate, lixivaptan, in patients with autosomal dominant polycystic kidney disease (ADPKD).

About Lixivaptan
Lixivaptan is an investigational, oral, nonpeptide selective vasopressin V2 receptor antagonist in development for the potential treatment of ADPKD. The development program is designed to show that lixivaptan can slow the decline in renal function that is typically observed in ADPKD patients while avoiding the liver safety issues associated with JYNARQUE®, a form of branded tolvaptan indicated for ADPKD, which is the only drug currently approved for ADPKD. Lixivaptan has been granted Orphan Drug Designation from the FDA.

About the ACTION Study
The ACTION Study is an ongoing two-arm Phase 3 pivotal trial consisting of a double-blind, placebo-controlled, randomized phase (Part 1) followed by a single-arm open-label phase (Part 2) to assess the efficacy and safety of lixivaptan in subjects with ADPKD.

In Part 1, all subjects will receive placebo and all subjects will receive lixivaptan to establish dosing. Up to 1,350 subjects will be randomized 2:1 to receive lixivaptan or placebo. After 52 weeks of randomized treatment, the administration of study drug will be paused, and final eGFR assessments for Part 1 will be obtained during three follow-up visits starting over a period of 28 days.

All subjects completing Part 1 are expected to continue into Part 2 of the study and be treated with the active drug, lixivaptan, for an additional 54-56 weeks. At the end of that time, study drug will be discontinued, and final eGFR assessments for Part 2 will be obtained during three follow-up visits starting over a period of 28 days. Further information on the study can be found at clinicaltrials.gov at the following link: https://clinicaltrials.gov/ct2/show/NCT04064346

About the ALERT Study
The ALERT Study is an ongoing open-label, repeat-dose study designed to assess liver and non-liver safety in subjects who previously experienced liver chemistry test abnormalities while treated with tolvaptan and were permanently discontinued from the drug for that reason. Subjects will be enrolled and treated with lixivaptan for 52 weeks following titration to an optimal dose. Further information on the study can be found at clinicaltrials.gov at the following link: https://clinicaltrials.gov/ct2/show/NCT04152837

About ADPKD
ADPKD is a rare hereditary disorder characterized by the formation and enlargement of cysts in the kidney, liver, and other organs. It is the fourth leading cause of kidney failure in the U.S. and one of the most common inherited genetic diseases in humans, occurring equally in women and men, in all races, globally. There are an estimated 140,000 diagnosed ADPKD patients in the U.S.

Forward Looking Statements
This press release contains forward-looking statements. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements, including statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the design, scope and purpose of our ongoing ALERT and ACTION studies; the development and therapeutic potential of our product candidates, including lixivaptan; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; and market size and opportunity for our product candidates.

Any forward-looking statements in this press release are based on our current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to our ability to protect and maintain our intellectual property position; business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oberland, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; future expenditures risks related to our asset-centric corporate model; the risk that any one or more of our product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and risks related to the COVID-19 pandemic including the effects of the Delta, Omicron and any other variants. These and other risks

concerning our programs and operations are described in additional detail in our most recent Form 10-Q, which is on file with the SEC. We explicitly disclaim any obligation to update any forward-looking statements except to the extent required by law.

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