Centessa Pharmaceuticals Demonstrates Proof-of-Mechanism from First Three PiMZ Subjects Dosed in Part B of Phase 1 Study Evaluating ZF874

November 1, 2021

~ First demonstration that a pharmacological chaperone can provide sufficient functional Z-A1AT increases to potentially achieve greater than 11 micromolar levels in individuals with PiZZ genotype ~

~ One subject with two-fold higher exposure experienced reversible ALT and AST elevations ~

~ Several actions underway to accelerate enrollment to refine dose and regimen for Phase 2 study expected to start in 2Q 2022 ~

~ Conference call and webcast scheduled for today at 8:30 a.m. EDT ~

BOSTON and LONDON, Nov. 01, 2021 (GLOBE NEWSWIRE) -- Centessa Pharmaceuticals plc ("Company") (Nasdaq: CNTA), together with subsidiary Z Factor Limited ("Z Factor"), today announced proof-of-mechanism data from the first three subjects dosed in the ongoing repeat dose Phase 1 Part B study of ZF874 in subjects carrying at least one Z-mutated alpha-1-antitrypsin allele (PiXZ). This is the first demonstration that a pharmacological chaperone can provide sufficient functional Z-A1AT increases to potentially achieve greater than 11 micromolar levels in individuals with the PiZZ genotype.

ZF-0101 is a Phase 1 study evaluating ZF874 (the "Study"), a novel, catalytically acting pharmacological chaperone designed to rescue the folding of the Z variant of alpha-1-antitrypsin ("A1AT") to address Alpha-1 Antitrypsin Deficiency ("AATD"). AATD is an autosomal recessive disorder frequently caused by missense mutations in the A1AT gene, resulting in the misfolding of A1AT. Individuals with AATD regularly suffer from chronic obstructive pulmonary disease and/or liver disease.

Part A of the Study was comprised of a single ascending dose study in 7 cohorts of healthy volunteers. Part B of the Study was initially designed to be a 28-day repeat dose study in up to 14 PiXZ patients (including 2 placebo), assessing the safety, tolerability and pharmacokinetics of ZF874. Increase in serum A1AT levels was an exploratory outcome.

In both PiMZ subjects dosed with 15 mg/kg BID of ZF874, the observed increase in functional A1AT was between 3.5 and 6 micromolar for these subjects with one Z-gene copy. The A1AT levels began to increase rapidly in the last week of dosing. After only 28 days of dosing the amount of A1AT was equivalent to achieving 12 to 17 micromolar in individuals with two Z- gene copies (PiZZ). In pre-clinical PiZ mouse models treated with ZF874, A1AT continues to rise with dosing beyond 28 days. A1AT plasma levels of 11 micromolar have been the basis for approval of the existing A1AT augmentation therapies. A1AT levels in the placebo-treated subject were not observed to change significantly.

Consistent with a pharmacological effect for ZF874, and as expected based on the circulating half-life of A1AT, levels returned to baseline by 28 days after completion of dosing.

Pharmacokinetic analysis showed a two-fold higher exposure to ZF874 in one subject. This subject showed a two-fold higher increase in functional A1AT as well as a delayed, reversible increase in ALT (8x ULN) and AST (3.5x ULN). All other liver function tests including bilirubin, GGT, and ALP remained in the normal range. All other adverse events reported in the Study were classified as mild. Due to ongoing enrollment challenges at the single clinical site, and following the observation of elevated liver enzymes in one Study participant, the Company elected to unblind the Study prior to completing Part B enrollment.

"With only two subjects of data, we have established proof of mechanism for ZF874 and show, for the first time, the promise of a catalytic small molecule corrector to restore A1AT to clinically significant levels," said Saurabh Saha, M.D., Ph.D., Chief Executive Officer of Centessa. "This now becomes a drug development exercise as we refine a dose and regimen for our planned global six-month Phase 2 study."

"These are exciting new findings. I look forward to hearing about further development of this novel approach, which has potential to treat both the lung and the liver in this complex disease," said Jeffrey Teckman, M.D., Patricia and James Monteleone Endowed Chair, Director, Pediatric Gastroenterology and Hepatology, Professor of Pediatrics and Biochemistry, Saint Louis University School of Medicine.

The Company is undertaking a number of actions to accelerate enrollment and facilitate dose exploration in PiXZ subjects, including opening additional sites in the UK and expanding the Study to the EU. In addition, the run-in portion of the expected Phase 2 study will be designed to further refine dose and regimen ahead of the start of 6-month dosing.

Conference Call and Webcast
Centessa Pharmaceuticals will host a webcast and conference call today, November 1, 2021, at 8:30 a.m. EDT to discuss interim results from Part B of the Study. To access the audio webcast with slides, please visit the "Events & Publications" page in the Investors & Media section of the Company's website at https://investors.centessa.com/events-presentations. The call can also be accessed by dialing (855) 493-3565 (domestic) or +1 (929) 517-9002 (international) with conference ID 3574786. An archive of today's webcast will be available on the Company's website.

About Centessa Pharmaceuticals
Centessa Pharmaceuticals plc 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 Z Factor Limited (Z Factor)
Z Factor is a clinical-stage biotechnology company founded in 2015 to identify and develop therapeutic agents to treat alpha-1-antitrypsin deficiency (“AATD”), a common genetic disorder where a single mistake in the DNA encoding the protein alpha-1-antrypsin (“A1AT”) causes both liver and lung disease.

Z Factor’s lead product candidate, ZF874, is a novel compound that acts as a pharmacological chaperone, allowing the Z variant of A1AT to fold correctly, thereby simultaneously relieving the liver burden of polymer accumulation and providing functional Z-A1AT in circulation to protect the lungs.

Forward Looking Statements
This press release has been prepared by Centessa Pharmaceuticals plc (the “Company”) for informational purposes only and not for any other purpose. This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements regarding our product candidates, including ZF874, its therapeutic potential and our development plans therefor, strategy, regulatory matters, including the timing and designed of planned clinical trials and our ability to complete certain milestones. Words such as "believe," "anticipate," "plan," "expect," "intend," "will," "may," "goal," "project," "estimate," "potential" and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of the Company's management as well as assumptions made by and information currently available to the Company. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including, without limitation, business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company, risks related to our ability to protect and maintain our intellectual property position; risks inherent in developing products and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing 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 business 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 variant and the other risk factors contained in our filings with the U.S. Securities and Exchange Commission. In light of these risks and uncertainties, the events or circumstances referred to in the forward-looking statements may not occur. The actual results may vary from the anticipated results and the variations may be material. These forward-looking statements should not be taken as forecasts or promises nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given.

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