Centessa Announces Positive Interim Phase 1 Clinical Data with its Novel Orexin Receptor 2 (OX2R) Agonist, ORX750, in Acutely Sleep-Deprived Healthy Volunteers

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- *2.5 mg dose restored normative wakefulness with mean sleep latency of 32 minutes as measured by the Maintenance of Wakefulness Test (MWT)*
- *Favorable safety and tolerability profile with no observations of frequently reported on-target adverse events (AEs) associated with other OX2R agonists, visual disturbances or hepatotoxicity as of the data cutoff date* [1]
- *PK profile supports once-daily dosing*
- *Company plans to rapidly initiate Phase 2 studies of ORX750 in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH)*

BOSTON and LONDON, Sept. 10, 2024 (GLOBE NEWSWIRE) -- Centessa Pharmaceuticals plc (Nasdaq: CNTA), a clinical-stage pharmaceutical company that aims to discover and develop medicines that are transformational for patients, today announced positive interim data from an ongoing Phase 1 trial of its highly potent and selective orexin receptor 2 (OX2R) agonist, ORX750, in acutely sleep-deprived healthy volunteers. ORX750 showed clinically meaningful and statistically significant improvements in mean sleep latency at the first two doses evaluated (1.0 mg and 2.5 mg) in the Maintenance of Wakefulness Test (MWT) compared to placebo. More specifically, the 2.5 mg dose was shown to restore normative wakefulness[2] with a mean sleep latency of 32 minutes as measured by the MWT. ORX750 was also shown to have a favorable safety and tolerability profile with no observations of frequently reported on-target adverse events (AEs) associated with other OX2R agonists, and no cases of hepatotoxicity or visual disturbances across all three dose levels tested (1.0 mg, 2.0 mg, and 2.5 mg), as of the data cutoff date.[1] Based on the interim data, the Company plans to rapidly advance ORX750 into Phase 2 studies in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) beginning in the fourth quarter of 2024.

“The Phase 1 acutely sleep-deprived healthy volunteer sleep study set a high bar for ORX750, and the early data generated has exceeded our expectations, giving us the confidence to accelerate the program into the next stage of clinical development earlier than anticipated,” said Saurabh Saha MD PhD, Chief Executive Officer of Centessa. “We are very pleased that the data support the potential for ORX750 to restore normative wakefulness in patients with NT1, NT2, and IH at very low, once-daily oral doses. Underpinning these data is a favorable initial safety and tolerability profile for ORX750, which provides us with the flexibility to explore the therapeutic potential of OX2R agonists. Given the strength of the data generated to date and the exciting potential opportunities we see with ORX750, we are aggressively pursuing our clinical development plans and expect to initiate Phase 2 studies of ORX750 in patients with NT1, NT2 and IH beginning in the fourth quarter of 2024.”

The Phase 1 clinical study is an ongoing first-in-human, randomized, placebo-controlled study designed to evaluate the safety, tolerability and pharmacokinetics (PK) of single-ascending doses (SAD) and multiple-ascending doses (MAD) of ORX750 in healthy adult subjects. In parallel to the SAD, a placebo-controlled cross-over pharmacodynamic (PD) assessment is being performed utilizing the MWT and Karolinska Sleepiness Scale (KSS) in acutely sleep-deprived healthy adult subjects with the goal of rapidly generating early efficacy data to inform dosing for planned studies in patients. As of September 10, 2024, the study has completed three SAD cohorts of healthy volunteers (27 active, 9 placebo) with doses of 1.0 mg, 2.0 mg, and 2.5 mg, and has advanced through two cohorts within the cross-over assessment of acutely sleep-deprived healthy volunteers with doses of 1.0 mg (n=8) and 2.5 mg (n=8), administered as a single oral dose. Dosing in the MAD portion of the study is also ongoing.

Summary of Data:
The interim Phase 1 clinical data for ORX750 demonstrated:

- Significantly increased wakefulness in acutely sleep-deprived healthy volunteers compared to placebo at both doses tested. Treatment with ORX750 resulted in statistically significant ($p<0.05$) and clinically meaningful increased sleep latency on the MWT (time to sleep onset over the four sessions performed at ~2, 4, 6, and 8 hours after dosing at 11 p.m., maximum 40 minutes per session) compared to placebo across all doses. Mean sleep latencies, as measured by the MWT, for 1.0 mg dose of ORX750 and placebo were 18 minutes and 10 minutes, respectively (p-value = 0.04) (least squares mean). Mean sleep latencies, as measured by the MWT, for 2.5 mg dose of ORX750 and placebo were 32 minutes and 17 minutes, respectively (p-value = 0.01) (least squares mean). The 2.5 mg dose was shown to restore normative wakefulness with a mean sleep latency of 32 minutes as measured by the MWT.
    - Favorable safety and tolerability observed as of the data cutoff date.[1]All observed treatment related AEs were mild and transient with none leading to treatment discontinuation.
    - No observations of frequently reported on-target AEs associated with other OX2R agonists, including urinary frequency, urinary urgency, insomnia, blood pressure increases, and salivary hypersecretion.
    - No cases of hepatotoxicity, visual disturbances or hallucinations were observed. Additionally, there were no clinically meaningful treatment-emergent changes in hepatic and renal parameters, vital signs, or electrocardiogram (ECG) parameters.
- Acutely sleep-deprived healthy volunteers who received a 2.5 mg dose of ORX750 showed a significant 1.6 point improvement versus placebo in mean KSS score compared to baseline (p-value = 0.03).
- Encouraging linear PK profile supports the use of ORX750 as a once-daily oral dosing regimen with rapid absorption (plasma concentrations of ORX750 peaked at 2h after the first dose). The systemic exposure of ORX750 increased in an approximately dose-proportional manner.

“With these interim data, we believe we have successfully demonstrated a potential best-in-class profile for ORX750 having achieved normative

wakefulness at once-daily low doses in subjects with normal orexin tone, coupled with a favorable safety and tolerability profile," said Mario Alberto-Accardi PhD, President, Centessa Orexin Program. "Consistent with what we've seen preclinically, we believe these data validate our unique structural biology driven orexin research platform and accelerate translation of our growing pipeline of orexin agonists, including the future development of ORX142, our second orexin agonist development candidate. We are excited to leverage these data to expedite the progression of our multi-asset orexin franchise to potentially treat sleep-wake disorders and excessive daytime sleepiness (EDS) across multiple conditions."

1. Data cutoff date of August 26, 2024.
2. Doghramji K, et al., A normative study of the maintenance of wakefulness test (MWT). Electroencephalogr Clin Neurophysiol 1997; 103:554-62.

About Centessa Pharmaceuticals
Centessa Pharmaceuticals plc is a clinical-stage pharmaceutical company that aims to discover and develop medicines that are transformational for patients. Our most advanced programs include a hemophilia program, an orexin agonist program for the treatment of narcolepsy and other sleep-wake disorders, and an immuno-oncology program focused on our LockBody® technology platform. We operate with the conviction that each of our programs has the potential to change the current treatment paradigm and establish a new standard of care. For more information, visit www.centessa.com, which does not form part of this release.

About Centessa's Orexin Agonist Program
Orexin is a neuropeptide that regulates the sleep-wake cycle, leading to arousal and promoting wakefulness. Low levels of orexin result in excessive daytime sleepiness (EDS) and poor regulation of rapid eye movement (REM) sleep and, in narcolepsy type 1 (NT1), cataplexy and other symptoms. Centessa is developing a pipeline of potential best-in-class orexin receptor 2 (OX2R) agonists, including ORX750 for the treatment of sleep-wake disorders, including NT1, narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH), and ORX142 for the treatment of EDS in select neurological, neurodegenerative, and psychiatric disorders. The Company's lead asset, ORX750, is in a Phase 1 clinical study. ORX750 and ORX142 have not been approved by the FDA or any other regulatory authority.

Forward Looking Statements
This press release contains forward-looking statements. These statements may be identified by words such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," "aim," "seek," 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 discover and develop transformational medicines for patients; its expectations for executing on the Company's pipeline; the timing of commencement of new studies or clinical trials or clinical and preclinical data related to ORX750; its ability to identify, screen, recruit and maintain a sufficient number of or any subjects in its existing and anticipated studies or clinical trials including in respect of ORX750; its expectations on executing its research and clinical development plans and the timing thereof; its expectations as to the potential results and impact of each of its clinical programs and trials; the Company's ability to differentiate ORX750 from other treatment options; the development, design and therapeutic potential of ORX750; and regulatory matters, including the timing and likelihood of success of obtaining regulatory clearance, obtaining authorizations to initiate or continue clinical trials. Any forward-looking statements in this press release are based on our current expectations, estimates, assumptions 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 the safety and tolerability profile of our product candidates, including ORX750; whether ORX750 could be shown to be ineffective; our ability to identify, screen and recruit a sufficient number of or any subjects in our existing and anticipated new studies or clinical trials including ORX750 or within anticipated timelines; our expectations relating to the further clinical development of ORX750 including initiation of phase 2 study and exploration of higher doses in the phase 1 study, including the predicted timing of enrollment, the predicted efficacious doses of ORX750 and our ability to successfully conduct our clinical development of ORX750; whether preclinical and initial clinical results for ORX750 will be predictive of results of further clinical trials; our ability to protect and maintain our intellectual property position; business (including commercial viability), regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing product candidates 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; our operating costs and use of cash, including cash runway, cost of development activities and conducting clinical trials, future expenditures risks; the risk that any one or more of our product candidates will not be successfully developed and/or commercialized; the risk that the historical results of preclinical studies or clinical studies will not be predictive of future results in ongoing or future studies; economic risks to the United States and United Kingdom banking systems; and geo-political risks such as the Russia-Ukraine war or the Middle East conflicts. These and other risks concerning our programs and operations are described in additional detail in our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and our other reports, which are on file with the U.S. Securities and Exchange Commission (SEC). We explicitly disclaim any obligation to update any forward-looking statements except to the extent required by law.

Contact:
Kristen K. Sheppard, Esq.
SVP of Investor Relations
investors@centessa.com