Centessa Pharmaceuticals Announces Preclinical Data Supporting ORX750's Potential as a Best-in-Class Oral OX2R Agonist for the Treatment of Narcolepsy and Other Sleep-Wake Disorders

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- Preclinical data demonstrated significant activity at low doses of ORX750 in highly predictive translational models of Narcolepsy Type 1 (NT1)

- ORX750 advancing in IND-enabling studies; Clinical proof of concept data planned for 2024

BOSTON and LONDON, Oct. 25, 2023 (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 a robust set of new preclinical data from *in vivo* and *in vitro* studies of its investigational, novel orexin receptor 2 (OX2R) agonist, ORX750, that support its potential best-in-class profile for the treatment of narcolepsy and other sleep-wake disorders.

The preclinical data will be featured today in an oral presentation by Sarah Wurts Black PhD, Head of Biology for Centessa's Orexin Agonist Program, entitled, "ORX750, an Oral Selective Orexin Receptor 2 Agonist, Promotes Wakefulness and Reduces Cataplexy in the Orexin/Ataxin-3 Mouse," at the World Sleep Congress in Rio De Janeiro, Brazil.

"We are very excited to share this robust preclinical dataset, which we believe shows the significant activity of low doses of ORX750 in highly predictive, translational models of narcolepsy type 1 (NT1)," said Mario Alberto Accardi PhD, President of Centessa's Orexin Agonist Program. "The preclinical data showed ORX750 achieved maximal wake times and suppressed cataplexy at 0.1 mg/kg, the lowest oral dose tested in the DTA mouse model. Notably, this activity was observed in both the DTA and Atax mouse models that recapitulate NT1 symptoms in humans. The data also showed ORX750 significantly increased wake time in healthy wild type mice at 1 mg/kg, the lowest oral dose tested, supporting the potential for expansion into broader sleep-wake disorders with normal orexin tone, including narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH). We believe these data highlight the breadth of ORX750's potential as a novel treatment for individuals living with narcolepsy and other sleep-wake disorders."

"ORX750 is a highly potent and selective novel orexin agonist that closely mimics the function of the endogenous peptide," said Saurabh Saha MD PhD, Chief Executive Officer of Centessa. "These preclinical data showed that ORX750 has the potential to address the underlying pathophysiology of orexin neuron loss in NT1 and promote wakefulness during the day and suppress cataplexy, including at levels that correspond to very low predicted human doses. In addition, the preclinical pharmacokinetic (PK) profile of ORX750, informed by PK testing in multiple species, including non-human primates, suggests the potential for ORX750 to have high, early and sustained brain exposure. We believe these data provide a strong translational foundation for clinical development. We are focused on rapidly moving ORX750 through IND-enabling studies, obtaining IND clearance and initiating clinical development of ORX750 with the goal of sharing clinical proof of concept data in 2024. We look forward to providing further updates in the coming months."

Overview of ORX750 Preclinical Results:

- ORX750 is a full OX2R agonist that potently activated the OX2R with an in vitro EC50 of 0.11 nM and 9,800-fold selectivity over the human orexin receptor (hOX1R)[1].
- In highly predictive, translational Atax and DTA mouse models, oral administration of ORX750 showed significant activity at the lowest dose tested, which was 0.1 mg/kg in a DTA mouse model, 0.3 mg/kg in an Atax mouse model, and 1 mg/kg in healthy wild type mice. ORX750:
    - Achieved maximal (100%) wake time for at least 3 hours post-dose;[2]
    - Suppressed cataplexy for at least 6 hours post-dose;[2]
    - Increased latency to sleep and cataplexy, which was maintained for >14 days of dosing;[3] and,
    - Increased consolidation of wakefulness.[4]

References: 1. Fluorescent imaging plate reader (FLIPR) assay with Chinese hamster ovary (CHO) cells stably expressing recombinant human OX1R or OX2R; OXA EC50 at hOX2R = 0.035 nM. 2. As measured by electroencephalogram (EEG) and electromyogram (EMG) with concurrent video in DTA and Atax mouse models. 3. As measured by EEG and EMG with concurrent video in Atax mouse model. 4. PiezoSleep assay as measured in DTA and Atax mouse models.

Centessa's preclinical data presentation for ORX750 will be available within a recorded webcast on the Company's website at https://investors.centessa.com/events-presentations immediately following the World Sleep presentation taking place at 10:45 a.m. BRT / 9:45 a.m. ET.

About ORX750
ORX750 is an investigational, orally administered, highly potent and selective orexin receptor 2 (OX2R) agonist designed to directly target the underlying pathophysiology of orexin neuron loss in narcolepsy type 1 (NT1). ORX750 is Centessa's first orexin product candidate being developed for the treatment of narcolepsy with potential expansion into other sleep-wake disorders. ORX750 is currently undergoing IND-enabling activities and has not been administered as an investigational drug to humans in any jurisdiction.

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 programs span discovery-stage to late-stage development and cover a range of high-value indications. We operate with the conviction that each one of our programs has the potential to change the current treatment paradigm and establish a new standard of care. For more information, visit http://www.centessa.com/, which does not form part of this release.

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 deliver transformational medicines to patients; the activity significance of low doses in highly predictive, translational models of narcolepsy type 1 (NT1) including maximal wake times and suppressed cataplexy at the lowest oral dose tested; the Company’s expectations on the timing of Ind-enabling studies of ORX750 in narcolepsy and other sleep-wake disorders; the ability of our management team and board to drive execution of the Company’s portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; the scope, progress, results and costs of developing our product candidates or any other future product candidates; our current expectations concerning, amongst other things, the development and therapeutic potential and benefits of our product candidates, including ORX750 and other OX2R agonists; strategy; regulatory matters, including the timing and likelihood of initiating clinical trials, reporting clinical trial results, ability to initiate or continue clinical trials or market any products; and the 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 the safety and tolerability profile of our product candidates including ORX750; 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; 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/or commercialized; and the risk that the results of non-clinical studies or clinical studies will not be predictive of future results in connection with future studies. 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