

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**
Washington, D.C. 20549

FORM 8-K

**CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Date of Report (date of earliest event reported): October 25, 2023

CENTESSA PHARMACEUTICALS PLC

(Exact name of Registrant, as specified in its charter)

England and Wales

(State or other jurisdiction of incorporation)

001-40445

(Commission File Number)

98-1612294

(I.R.S. Employer Identification Number)

Mailing address:

3rd Floor

1 Ashley Road

Altrincham

Cheshire WA14 2DT

United Kingdom

(Address of principal executive offices) (Zip code)

Registrant's telephone number, including area code: **+44 7391 789784**

Former name or address, if changed since last report:

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value £0.002 per share	CNTA	Nasdaq Stock Market, LLC*
American Depositary Shares, each representing one ordinary share, nominal value £0.002 per share	CNTA	Nasdaq Stock Market, LLC

*Not for trading, but only in connection with the listing of the American Depositary Shares on The Nasdaq Stock Market, LLC.

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 7.01 Regulation FD Disclosure

On October 25, 2023, Centessa Pharmaceuticals plc (the “Company”) presented preclinical data from *in vivo* and *in vitro* studies of its investigational orexin receptor 2 (OX2R) agonist, ORX750 at World Sleep 2023. The presentation materials are attached to this Current Report on Form 8-K as Exhibit 99.1.

Additionally, the Company issued a press release titled “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.” A copy of the press release is furnished as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information under this Item 7.01, including Exhibits 99.1 and 99.2 hereto, is being furnished and shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On October 25, 2023, the Company announced new preclinical data from *in vivo* and *in vitro* studies of its investigational, novel orexin receptor 2 (OX2R) agonist, ORX750, being investigated for the treatment of narcolepsy with potential expansion into other sleep-wake disorders.

The following preclinical data introduce the preclinical profile of ORX750 as the basis for its selection as a development candidate for the treatment of narcolepsy with potential expansion into other sleep-wake disorders.

- ORX750 potently activated the OX2 receptor with an *in vitro* EC₅₀ of 0.11 nM for human recombinant OX2R (hOX2R)¹.
- In highly predictive, translational orexin/TA;TetO diphtheria toxin fragment A or “DTA” mouse model and an orexin/ataxin-3 or “Atax” mouse model, 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, 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.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	ORX750 Preclinical Data Presentation from World Sleep 2023 on October 25, 2023
99.2	Press Release dated October 25, 2023
104	Cover Page Interactive Data (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: October 25, 2023

By: /s/ Saurabh Saha
Name: Saurabh Saha, M.D., Ph.D.
Title: Chief Executive Officer

Disclaimer

This presentation has been prepared by Centessa Pharmaceuticals plc (the "Company") for informational purposes only and not for any other purpose. This presentation does not contain all the information that is or may be material to investors or potential investors and should not be considered as advice or a recommendation to investors or potential investors in respect of the holding, purchasing or selling of securities or other financial instruments and does not take into account any investor's particular objectives, financial situation or needs. The communication of this presentation may be restricted by law, it is not intended for distribution to, or use by any person in, any jurisdiction where such distribution or use would be contrary to local law or regulation. This presentation is not directed to or intended for distribution, or transfer, either directly or indirectly to, or use by, any person or entity that is a citizen or resident or located in any locality, state, country or other jurisdiction where such distribution, transfer, publication, availability or use would be contrary to law or regulation or which would require any registration or licensing within such jurisdiction.

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 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; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including ORX750 and other orexin agonist molecules; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; enroll subjects in clinical trials; market size and opportunity for our product candidates; and our anticipated cash runway. 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 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, 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, geopolitical risks such as the Russia-Ukraine conflict and 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. All projections, valuations and statistical analyses are provided for information purposes only. We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward looking statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances on which any such statement is based, except as may be required by law. They may be based on subjective assessments and assumptions and may use one among alternative methodologies that produce different results and to the extent they are based on historical information, they should not be relied upon as an accurate prediction of future performance.

This presentation discusses product candidates that are under clinical study, and which have not yet been approved for marketing by the U.S. Food and Drug Administration or any other regulatory agency. No representation or warranty, express or implied, is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third party sources and the Company's own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation or warranty, express or implied, as to the adequacy, fairness, accuracy or completeness of, any information obtained from third party sources. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.



**ORX750, an Oral Selective Orexin Receptor 2
Agonist, Promotes Wakefulness and Reduces
Cataplexy in the Orexin/Ataxin-3 Mouse**

Sarah Wurts Black, Ph.D.

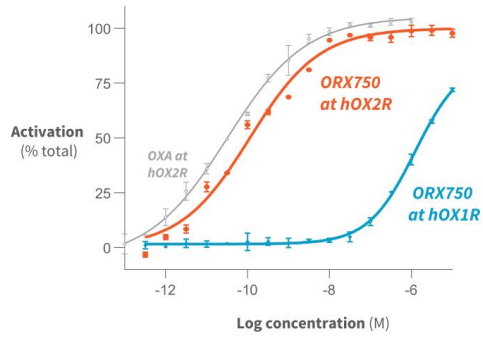
October 25th
World Sleep 2023, Rio de Janeiro, Brazil

Executive summary

- **ORX750 is a novel, full OX2R agonist** designed using high resolution crystal and cryo-EM structures
- **ORX750 potently activated the OX2R with an EC₅₀ of 0.11 nM and 9,800-fold selectivity over OX1R**
- **Oral administration of ORX750 achieved maximal wake times in highly predictive Atax and DTA mouse models of narcolepsy type 1**
 - **Activity observed at 0.1 mg/kg**, the lowest dose tested in DTA mice
 - Increased time awake, latency to sleep, latency to cataplexy, and consolidation of wakefulness
 - Suppressed cataplexy occurrences
- **ORX750 showed activity in wild type mice** at the lowest dose tested (1 mg/kg)



ORX750 showed high *in vitro* potency at OX2R and selectivity vs. OX1R



EC₅₀ 0.11 nM for hOX2R
9,800-fold selectivity vs. hOX1R

- Activation pattern was indistinguishable from OXA with lack of biased agonism¹
- No significant differences in OX2R potency were observed across species²
- No significant pharmacological activity observed in GPCR selectivity and *in vitro* safety panels³



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; ORX750 EC₅₀ at hOX1R = 1100 nM

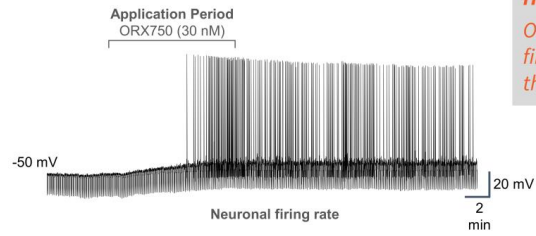
¹ PathHunter β-arrestin recruitment assay with CHO cells co-expressing ProLink™ (PK)-tagged OX2R and Enzyme Acceptor (EA)-tagged β-arrestin

² Human, mouse, rat, dog, monkey recombinant receptors *in vitro*

³ Safety 47 and GPCRMax168 from >60 receptor families

ORX750 activated endogenous OX2R in mouse *ex vivo* brain slice

Whole cell recordings of histaminergic neurons in ventral TMN in mouse brain slices



High potency at native mouse OX2R

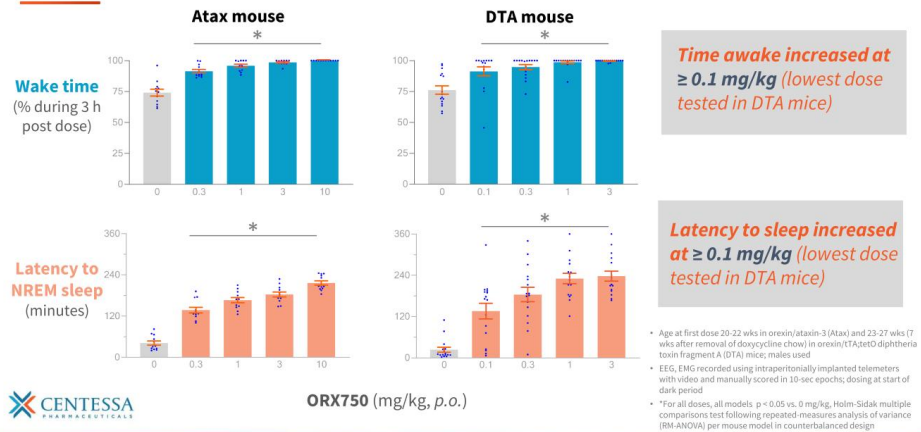
ORX750 depolarized¹ and increased firing rates² of histaminergic neurons in the TMN



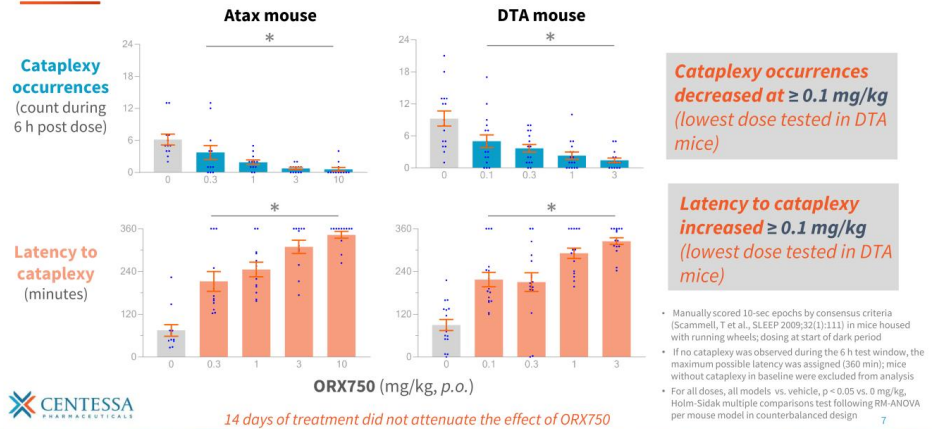
- ORX750 EC₅₀ 5 nM; OXA EC₅₀ 32 nM
- TMN=tuberomammillary nucleus, area enriched in OX2R and a component of the orexinergic wake-promoting neurocircuitry (Mignot, E., et al., Front Neurol Neurosci, 2021;45:103)

1. Performed in presence of tetrodotoxin
2. Performed in absence of tetrodotoxin

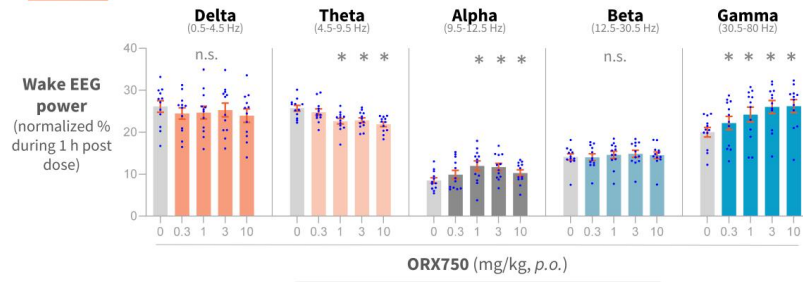
ORX750 promoted wakefulness in NT1 mouse models during the active phase in the EEG/EMG/video assay



ORX750 suppressed cataplexy in NT1 mouse models during the active phase in the EEG/EMG/video assay



ORX750 altered EEG power during wakefulness during the active phase in Atax mice

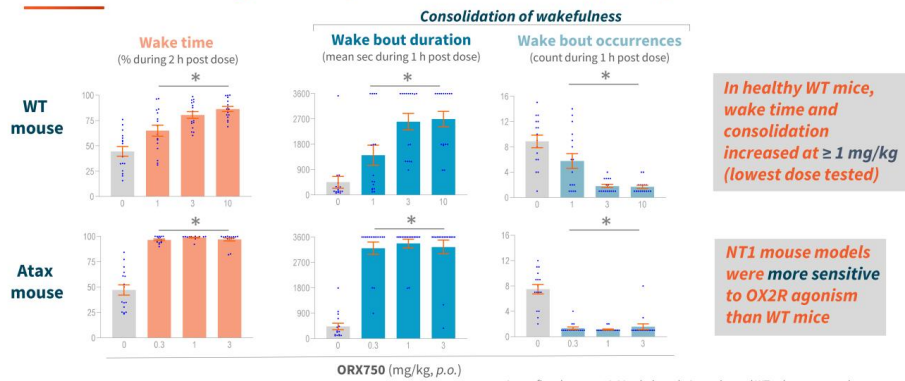


ORX750 increased EEG power during wakefulness in the alpha and gamma bands and decreased power in the theta band



- Increase in EEG power in gamma frequency associated with enhanced alertness (Cantero, J.L., et al., NeuroImage, 2004;22:1271)
- Data normalized as the percent of the mean power across all frequency bands in 6 h recording from 10-sec, artifact-free wakefulness epochs of manually scored EEG
- * p < 0.05 vs. 0 mg/kg, Holm-Sidak multiple comparisons test following RM-ANOVA in counterbalanced design

ORX750 increased wake time and consolidation in wild type (WT) and an NT1 mouse model during the rest phase in the PiezoSleep assay



* Data collected using PiezoSleep, in which wakefulness readouts based on movement & breath rate highly correlate with EEG/EMG measures (Black, et al., ERS2022 presentation)

- Age at first dose was 16-20 wks in male Atax mice and WT colony mates; mice dosed at 5 h after lights on
- * $p < 0.05$ vs. 0 mg/kg, Holm-Sidak multiple comparisons test following RM-ANOVA per mouse model in counterbalanced design

Summary and conclusion

- **ORX750 is a novel, full OX2R agonist** designed using high resolution crystal and cryo-EM structures
- **ORX750 potently activated the OX2R with an EC₅₀ of 0.11 nM** and 9,800-fold selectivity over OX1R
- **Oral administration of ORX750 achieved maximal wake times in highly predictive Atax and DTA mouse models of narcolepsy type 1**
 - **Activity observed at 0.1 mg/kg**, the lowest dose tested in DTA mice
 - Increased time awake, latency to sleep, latency to cataplexy, and consolidation of wakefulness
 - Suppressed cataplexy occurrences
- **ORX750 showed activity in wild type mice** at the lowest dose tested (1 mg/kg)

We believe these results support further progression of ORX750 as a potential best-in-class treatment for narcolepsy and other sleep/wake disorders

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

- *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, October 25, 2023: [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](http://www.centessa.com/) 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:

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investors@centessa.com